



201 Menlo Drive
Santa Barbara, CA 93111 USA

(805) 879-5000

www.mentorcorp.com

August 6, 2003

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, MD 20850

RE: PMA M020018/M3 Mentor Low-Bleed Gel-Filled Mammary Prosthesis:
Module #3 Chemistry Data

Mentor Corporation is submitting Module #3 of the above-referenced PMA in order to provide Chemistry test data for Mentor's Low-Bleed Gel-Filled Mammary Prostheses.

We consider the existence of this submission and its contents to be confidential and exempt from public disclosure.

If additional information is needed, please contact Donna Crawford at (805) 879-6304.

Sincerely,

A handwritten signature in cursive script that reads "Donna Free".

Donna Free
Vice President, Regulatory Submissions

2005-410101-01-03-CHEMISTRY DATA-MENTOR



**LOW-BLEED GEL-FILLED
MAMMARY PROSTHESIS PMA
CHEMICAL TESTING**

July 30, 2003

TABLE OF CONTENTS

1.0	EXECUTIVE SUMMARY	1
2.0	INTRODUCTION & TESTING RATIONALE	2
3.0	DEVICE DESCRIPTION & RAW MATERIALS	5
4.0	SILICONE CHEMISTRY	11
4.1	Shell Fabrication	11
4.2	Texturing Shells	12
4.3	Fabrication & Attachment of Patch to Shell	13
4.4	Laser Marking, Gel-Fill & Curing to Final Gel	14
4.5	Conclusions	15
4.5.1	Shell	15
4.5.2	Texture & Patch	16
4.5.3	Gel	16
5.0	CHEMICAL ANALYSIS	28
5.1	Volatile Components	30
5.1.1	Shell	31
5.1.2	Gel Filler	32
5.1.3	Whole Device	32
5.1.4	Conclusions	32
5.2	Extractables Analysis on Shell & Gel from Devices that are the Subject of this PMA Submission	34
5.2.1	Total Extractables Analysis	34
5.2.2	Semivolatiles Analysis	35
5.2.2.1	Shell	35
5.2.2.2	Gel	36
5.2.2.3	Whole Device	36
5.2.2.4	Conclusion	36
5.2.3	Nonvolatiles Analysis	38
5.2.3.1	Gel	38
5.2.3.2	Shell	39
5.2.3.3	Conclusion	39
5.3	Sol Fraction, Equilibrium Swell Ratio and Cross link Density	41
5.3.1	Gel	42
5.3.2	Shell	42
5.3.3	Conclusion	43

5.4	Heavy Metals	43
5.4.1	Platinum	46
5.4.1.1	Platinum Determination	46
5.4.1.2	The Chemical Nature of Residual Platinum in Silicone Breast Implants from Published Literature	47
5.5	Infrared Spectral Analysis	50
5.6	Silicone Fluid Component of Gel Formation	51
5.7	Physical Properties of the Gel	51
5.8	Chemical Characterization of Laser-Marked Patches	51
5.8.1	Optical Microscopy	52
5.8.2	Infrared Spectroscopy	52
5.8.3	Gas Chromatography / Mass Spectrometry	59
5.8.4	Organic Elemental Analysis	59
5.8.5	X-Ray Diffractometry	59
5.8.6	X-Ray Photoelectron Spectroscopy	60
5.8.7	Raman Spectroscopy	60
5.8.8	Conclusion	61
5.9	Alternate Mandrel Material Composition	61
5.9.1	Total Extractable Content	62
5.9.2	Semivolatiles Content	63
5.10	Chemical Characterization Comparison Between Devices Covered by this Submission & Devices Previously Manufactured by Mentor Corporation	64
5.10.1	Volatiles Analysis	65
5.10.1.1	SiTech, Dow Corning & ASC Gels	65
5.10.1.2	Comparison of Shells From PTC & SiTech Dispersion	67
5.10.2	Extractables Content	68
5.10.2.1	Total Extractables Comparison of Dow Corning, SiTech, and ASC Gel	68
5.10.2.2	Total Extractable Content Comparison of Shells from PTC & SiTech Dispersion	68
5.10.3	Semivolatile Content of Extractables	69
5.10.3.1	Change in Semivolatiles Method of Analysis	70
5.10.3.2	Semivolatiles Comparison of Dow Corning, SiTech, and ASC Gel	80
5.10.3.3	Semivolatile Extractable Compounds of PTC Elastomer Shells & SiTech Elastomer Shells	85
5.10.4	Nonvolatiles Content of Extractables	87

5.10.4.1	Nonvolatile Content Comparison of Dow Corning Gel, SiTech, and ASC Gel	87
5.10.4.2	Comparison of Nonvolatile Extractable Content Between PTC Raw Material Shells and SiTech Raw Material Shells	88
5.10.5	Extent of Crosslinking, Swell Ratios, and Percent Extractables	91
5.10.5.1	Extent of Crosslinking Comparison of Dow Corning, SiTech, and ASC Gel	91
5.10.5.2	Extent of Crosslinking Comparison of PTC and SiTech Shells	92
5.10.6	Heavy Metals	93
5.10.6.1	Heavy Metals Content of Dow Corning, SiTech and ASC Gel	93
5.10.6.2	Heavy Metals Content of PTC Shells & SiTech Shells	94
5.10.7	Infrared Spectral Analysis	96
5.10.7.1	IR of Dow Corning & SiTech Gels	96
5.10.7.2	Infrared Spectral Analysis of PTC & SiTech Shells with NuSil & SiTech Texture Layers & Shell Patches	98
5.11	Solvent Selection for Extractions on Samples from Finished Device	100
6.0	TOXICITY RISK ANALYSIS	101
6.1	Metals	103
6.1.1	Beryllium	103
6.1.2	Magnesium	103
6.1.3	Titanium	103
6.1.4	Vanadium	104
6.1.5	Chromium	104
6.1.6	Cobalt	104
6.1.7	Nickel	104
6.1.8	Copper	105
6.1.9	Zinc	105
6.1.10	Arsenic	105
6.1.11	Selenium	105
6.1.12	Molybdenum	106
6.1.13	Silver	105
6.1.14	Cadmium	106
6.1.15	Tin	106
6.1.16	Antimony	106
6.1.17	Barium	106
6.1.18	Platinum	107
6.1.19	Mercury	107
6.1.20	Lead	108

6.2	Siloxanes	108
6.2.1	D ₄ (octamethylcyclotetrasiloxane)	108
6.2.2	D ₅ (decamethylcyclopentasiloxane)	109
6.2.3	- - - - -	110
6.3	Aromatics	111
6.3.1	Xylene	111
7.0	SUMMARY AND CONCLUSION	112

LIST OF FIGURES

Figure 2-1	Device Testing Scheme	4
Figure 3-1	Smooth Round Gel-Filled Mammary Implant	9
Figure 3-2	Siltex Round Gel-Filled Mammary Implant	10
Figure 4-1	Reaction of Hexamethyldisilazane with Surface Silanol Units	18
Figure 4-2	Key to Nomenclature Used in Chemical Equations	19
Figure 4-3	Hydrosilylation Mechanism (Additional Reaction)	20
Figure 4-4	Chemistry of Shell Dimethyl Layer Cure	21
Figure 4-5	Chemistry of Shell ----- Cure	21
Figure 4-6	Chemistry of Texturing and Patch Cure	22
Figure 4-7	Chemistry of Cure of RTV Dispersion Sealant for Hole Left by Gel Precursor Injection Needle	23
Figure 4-8	Chemistry of Gel Curing	25
Figure 4-9	Potential Candidates for Analytical Quantification Based Upon Chemistry	26
Figure 5-1	IR Spectra Overlay of Siltex Shell from Siltex Round Gel Mammary Implant and Dimethylsiloxane	53
Figure 5-2	IR Spectra Overlay of Inner Surface Siltex Shell from Siltex Round Gel Mammary Implant and Dimethylsiloxane	54
Figure 5-3	IR Spectral Comparison of Laser Marked and Unmarked Areas of Siltex Round Gel Mammary Implant	55
Figure 5-4	IR Spectra Overlay of Dipcoat Reinforcement from Siltex Round Gel Mammary Implant and Dimethylsiloxane	56
Figure 5-5	IR Spectra Overlay of Gel Filler from Siltex Round Gel Mammary Implant and Dimethylsiloxane	57

LIST OF FIGURES (Cont'd.)

Figure 5-6	IR Spectra Overlay of Patch from Siltex Round Gel Mammary Implant and Dimethylsiloxane	58
Figure 5-7	Comparison of Analytical Results on Cyclic Dimethylsiloxane in Gel Filler Samples as Determined by Old GC Instrument Employing Original and Additional Calibration Standards and New GC Instrument Employing Additional Calibration Standards	74
Figure 5-8	Comparison of Analytical Results on Linear Dimethylsiloxane Compounds in Gel Filler Samples as Determined by Old GC Instrument with Original and New Calibration Standards and New Instrument with Additional Calibration Standards	79
Figure 5-9	Extractable Cyclic Siloxane Comparison of SiTech, Dow Corning, and ASC Gels (New Versus Old Methodology)	84
Figure 5-10	IR Spectral Comparison of Gel Fillers from Siltex Round Low-Bleed Devices (Dow, ASC and SiTech)	97
Figure 5-11	IR Spectral Comparison of HTV Smooth Shell (PTC vs. SiTech)	99

LIST OF TABLES

Table 3-1	Gel-Filled Mammary Prostheses Raw Materials	6
Table 5-1	Summary of Vendors for Device Components	28
Table 5-2	Volatile Compounds in Siltex Round Moderate Profile Gel-Filled Mammary Implants (SiTech Texture Layer, Shell and Gel Filler)	33
Table 5-3	Total Extractables on a Nongelled Shell and Calculated for a Whole Device (SiTech Textured Layer, Shell, and Gel Filler Materials)	35
Table 5-4	Semivolatiles Results on Siltex Round Moderate Profile Gel-Filled Mammary Implants (SiTech Raw Materials for Texture Layer, Shell and Gel Filler)	36
Table 5-5	Nonvolatile Extractables Analysis of Gel Filler from Siltex Round Moderate Profile Gel Mammary Implants	40
Table 5-6	Nonvolatiles Extractables Analysis of Shell Samples from Siltex Round Moderate Profile Gel Mammary Implants	40
Table 5-7	Nonvolatiles Analysis of Nongelled Shell from Siltex Round Moderate Profile Gel Mammary Implants	41
Table 5-8	Nonvolatile Extractable Compound Concentration of Nongelled Shell from Siltex Round Moderate Profile Shells	41
Table 5-9	Crosslink Density, Swell and Extractables of Gel and Shell Samples from Siltex Round Moderate Profile Gel Mammary Implants	43
Table 5-10	Heavy Metals Analysis of Devices Made with SiTech Gel and Shell	44
Table 5-11	Worst Case Heavy Metals Content in SiTech Gel, SiTech Shells, and Complete Devices	45
Table 5-12	Characteristic Absorbances of Poly Dimethyl Siloxane Materials	50
Table 5-13	Organic Elemental Analysis of Laser Marked and Unmarked Silicone Elastomer	59
Table 5-14	XPS Elemental Analysis of Laser Marked and Unmarked Silicone Elastomer	60

LIST OF TABLES (Cont'd.)

Table 5-15	Comparison of Total Extractables in Shell Assemblies from Ertalyte and Teflon Coated Stainless Steel Mandrels	62
Table 5-16	Comparison of Semivolatile Extractables in Shell Assemblies from Ertalyte and Teflon Coated Stainless Steel Mandrels	63
Table 5-17	Volatile Analysis of Dow Corning, SiTech and ASC Gel	66
Table 5-18	Extractable Volatile Compounds from PTC Shells Versus SiTech Shells	67
Table 5-19	Total Extractables from SiTech, Dow Corning, and ASC Gel	68
Table 5-20	Comparison of Total Extractable Results from Shell Assemblies Made with Materials from Different Vendors	69
Table 5-21	Semivolatile Extractables from Siltex Round Moderate Profile Gel-Filled Mammary Implants (Lot #188747) – Different Gas Chromatographs and Calibration Standards	75
Table 5-22	Semivolatile Extractable Content Comparison of SiTech, Dow Corning, and ASC Gel	82
Table 5-23	Semivolatiles Extractable Content Comparison of PTC and SiTech Nongelled Shells	86
Table 5-24	Polysiloxane Molecular Weight Comparison of Dow Corning, SiTech, and ASC Gel Samples by GPC/RI Detector	88
Table 5-25	Nonvolatile Compounds in Finished Gel-Filled Mammary Prostheses Shells	88
Table 5-26	Nonvolatile Compounds in Nongelled Low-Bleed Shells	90
Table 5-27	Comparisons of Dow Corning, SiTech, and ASC Gel Crosslinking, Swell Ratios and Percent Extractables	92
Table 5-28	PTC Shell/NuSil Texture, SiTech Shell/NuSil Texture, and SiTech Shell/SiTech Texture Crosslinking, Swell Ratio and Percent Extractables	93
Table 5-29	Heavy Metal Analysis of Dow Corning, SiTech, and ASC Gels	94
Table 5-30	Heavy Metals Analysis of SiTech and PTC Shells	95

LIST OF TABLES (Cont'd.)

Table 5-31	Extraction Solvent Comparison of ASC Gel from Siltex Round Low-Bleed Devices: Direct Gravimetric Weight Measurement Results	101
Table 5-32	Extraction Solvent Comparison of PTC Shells from Siltex Round Low-Bleed Devices: Direct Gravimetric Weight Measurement Results	101

LIST OF APPENDICES

	<u>Vol.</u>	<u>Page</u>
Appendix 1		Material Safety Data Sheets
Appendix 2		Curriculum Vitae for Professor Robert A. Scott
Appendix 3		Critical Evaluation of the Pharmacokinetic Model for D4 Developed by Luu and Hutter (by Harvey Clewell III)
Appendix 4		Curriculum Vitae for Harvey Clewell III
Appendix 5	CP273I	Crosslink Density, Sol Fraction and Equilibrium Swell Ratio of Gel-Filled Mammary Prosthesis Gel
Appendix 6	CP273II	Crosslink Density, Sol Fraction and Equilibrium Swell Ratio of Gel-Filled Mammary Prosthesis Shell
Appendix 7	CP274I	Extraction Solvent Comparison of Gel-Filled Mammary Prosthesis Gel
Appendix 8	CP274II	Extraction Solvent Comparison of Gel-Filled Mammary Prosthesis Shell
Appendix 9	CP278I	GPC Analysis of Nonvolatile Extractables from Gel-Filled Mammary Prosthesis Gel
Appendix 10	CP278II	GPC Analysis of Nonvolatile Extractables from Gel-Filled Mammary Prosthesis Shell
Appendix 11	CP279	Heavy Metals Analysis of Gel-Filled Mammary Prosthesis
Appendix 12	CP280	Surface Chemical Composition of DOW, ASC, and SiTech Gel-Filled Mammary Prosthesis
Appendix 13	CP290	Total Extractables Analysis of Gel-Filled Mammary Prosthesis: SiTech Raw Material Vendor Qualification
Appendix 14	CP291	Nonvolatile Extractables Analysis of Gel-Filled Mammary Prosthesis: SiTech Raw Material Vendor Qualification
Appendix 15	CP292	Semivolatile Extractable Analysis of Gel-Filled Mammary Prosthesis: SiTech Raw Material Vendor Qualification

LIST OF APPENDICES (Cont'd.)

Appendix 16	CP293	Volatile Extractables Analysis of Gel-Filled Mammary Prosthesis: SiTech Raw Material Vendor Qualification
Appendix 17	CP333	Total and Semivolatile Extractable Analysis of Gel-Filled Mammary Prosthesis: Teflon/Stainless Steel Shell Mandrel Qualification
Appendix 18	CP351	Semivolatile Extractables Analysis of Gel Mammary Implant: Comparison of Instruments and Quantitation Methods
Appendix 19	CP353	Chemical Testing of Laser Marked Patches for Mammary Implants
Appendix 20	CP357	Total and Semivolatile Extractables Analyses of Gel Mammary Implants: Qualification of Manufacturing Process Modifications
Appendix 21	CP358	Volatile Extractables Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications
Appendix 22	CP359	Nonvolatile Extractables Analysis of Gel Mammary Implant: Qualification of Manufacturing Process Modifications
Appendix 23	CP360	Extractable Metals Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications
Appendix 24	CP361	Sol Fraction, Equilibrium Swell Ratio and Crosslink Density of Gel Mammary Implants: Qualification of Manufacturing Process Modifications
Appendix 25	CP362	Infrared Spectral Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications

1.0 EXECUTIVE SUMMARY

This Mentor PMA Application for Low-Bleed Gel-Filled Mammary Prostheses covers three product lines – Moderate Profile Gel, Moderate Plus Profile Gel and High Profile Gel all in both smooth and Siltex shell surfaces. The product lines differ in their amount of projection and width but are all fabricated using the same materials, basic components, and processes. An overview of the devices including raw materials, shapes, volumes and detailed drawings can be found in Section 3.0 Device Description. This module presents the Chemistry data in support of these products.

The design and construction of Mentor's current Low-Bleed Gel-filled Mammary Prosthesis, is substantially the same as when Mentor first began marketing the device in 1985. Over the nearly twenty years of its manufacture, Mentor has accumulated a very extensive body of preclinical and clinical data on this device. This device and its major components are currently manufactured from raw materials (intermediates) supplied by SiTech LLC (texture layer, elastomer shell and gel filler). This PMA module presents the chemistry test results obtained for Mentor's Gel-filled Mammary Prosthesis and its major components, and includes extensive recent testing on finished devices manufactured from SiTech materials and incorporating recent manufacturing changes. The chemistry testing was performed in accordance with FDA's Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Guidance for Industry and FDA (February 11, 2003).

The data from such testing provided the primary basis for a biomaterials toxicity risk assessment of potentially extractable chemical compounds from this device. Chemical analysis provided quantitative information for a wide range of metals, as well as siloxanes and solvents. These levels were compared where possible to established health risk-based standards, toxicity threshold levels identified in the published literature, and/or levels known to normally be present in the human body. The results of the biomaterials toxicity risk analysis demonstrated that, under conservative worst-case conditions, none of the levels of extractables identified during Mentor's testing exceed any recognized toxicity standard and/or level normally known to be present in the body. Thus, the extractables identified in the Mentor Gel-filled Mammary Prostheses should not present a health risk if they were to exit from the implanted devices.

A wide range of compounds have been studied by Mentor. Historically, two compounds of significance have been reported in the literature, one compound being platinum and the other compound being D₄ (octa-methylcyclotetrasiloxane). Platinum from the device is not only below accepted toxicity limits (as determined by the biomaterials toxicity risk assessment), but published literature provides strong evidence that the platinum catalyst is present in the zero valence state at the end of the reaction, after curing (based on the mechanism of the silicone synthesis hydrosilation reactions). This valence state is the least toxic of all the platinum valence states. Details for other analyzed metals are provided in the body of this PMA module.

The amount of D₄ (octamethylcyclotetrasiloxane) in Mentor Gel-filled Mammary Prosthesis was determined to be very low. The estimated reasonable worst-case daily exposure, when expressed on a body weight basis, is orders of magnitude below levels that have been demonstrated to have

no adverse effects in experimental animals. Details for other analyzed siloxanes are provided in the body of this PMA module.

The levels of potentially extractable materials were also compared to extensive data on components from previously manufactured Mentor devices fabricated from previous vendors' intermediates. Such comparisons were performed to confirm that long-term biological safety testing (i.e., chronic toxicity/carcinogenicity, reproductive and developmental toxicity, immunotoxicity) performed on Mentor gel-filled mammary devices and components made with those intermediates was still directly applicable to the devices in this PMA submission. Specifically, the data comparisons clearly demonstrated the substantial equivalence of gel fillers produced from SiTech and from Dow Corning intermediates, as well as the substantial equivalence of shells produced from SiTech and from Polymer Technology Corporation intermediates, as evidenced by: 1) the amount of extractables from shells and gels, 2) the qualitative and quantitative chemical characterization of the individual compounds in those extractables; 3) surface characterization; and 4) heavy metals analysis and crosslink density. (These silicone raw materials have previously been demonstrated to be not substantially different in accordance with FDA guidelines, and as documented in vendor Master Access Files.)

Extractables analysis was also performed on the previously utilized gel filler from Applied Silicone Corporation (ASC). Levels of low molecular weight cyclic siloxanes were higher than for SiTech and Dow Corning gels. The ASC gel also successfully passed long-term biological safety testing.

The data presented and summarized in this chemistry PMA module for Mentor's Gel-filled Mammary Prostheses strongly supports the safety of this device for its intended use.

2.0 INTRODUCTION AND TESTING RATIONALE

This module of Mentor's Low-Bleed Gel-filled Mammary Prosthesis PMA describes the chemical testing performed on sterile finished devices or components of sterile finished devices. The information is provided to identify and quantify extractable compounds from mammary prostheses. The selection of tests, assurance of the accuracy and precision of those tests and the actual generation of analytical data conform to the requirements outlined in FDA's "Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Guidance for Industry and FDA" (issued February 11, 2003). Finally, the data are used to confirm that no potential contaminants are present in the finished product at an unacceptably high level.

Gravimetric analysis of residues from a solvent extraction was used to determine total extractables from gel filler and shell samples. Instrumental analyses for compositional constituents of the extractables from the gel filler and the shell yielded concentrations of specific extractable compounds. These concentrations of specific compounds from both the shell and gel were mathematically combined to provide a characterization of a whole device. Analytical techniques employed included dynamic headspace purge/trap with gas chromatography/mass spectroscopy for volatile compounds, direct liquid injection gas chromatography/mass spectroscopy detection for semivolatile compounds in extraction solutions, and gel permeation

chromatography with refractive index and spectrophotometric detection for nonvolatile compounds in extraction solutions. Extractable compounds with molecular weight less than 1500 were separated, detected, and quantified.

In addition to the above extract testing, determination of extractable heavy metals, device component crosslink densities, and surface composition analysis were conducted. Where appropriate, a solvent extraction comparison and verification of exhaustive solvent extraction were performed. All sample preparation and analysis methods were validated by including spiked recovery of selected analytes and assessment of quantification methods for linearity, precision, and detection limits. (All recovery, validation, linearity, and detection limit data can be found in the individual reports.) Reference libraries of standard compounds were developed from consideration of raw materials, additives, synthesis byproducts and manufacturing process aids and were used for positive identification of extractable compounds.

A schematic summary of the chemical testing is presented in Figure 2-1.

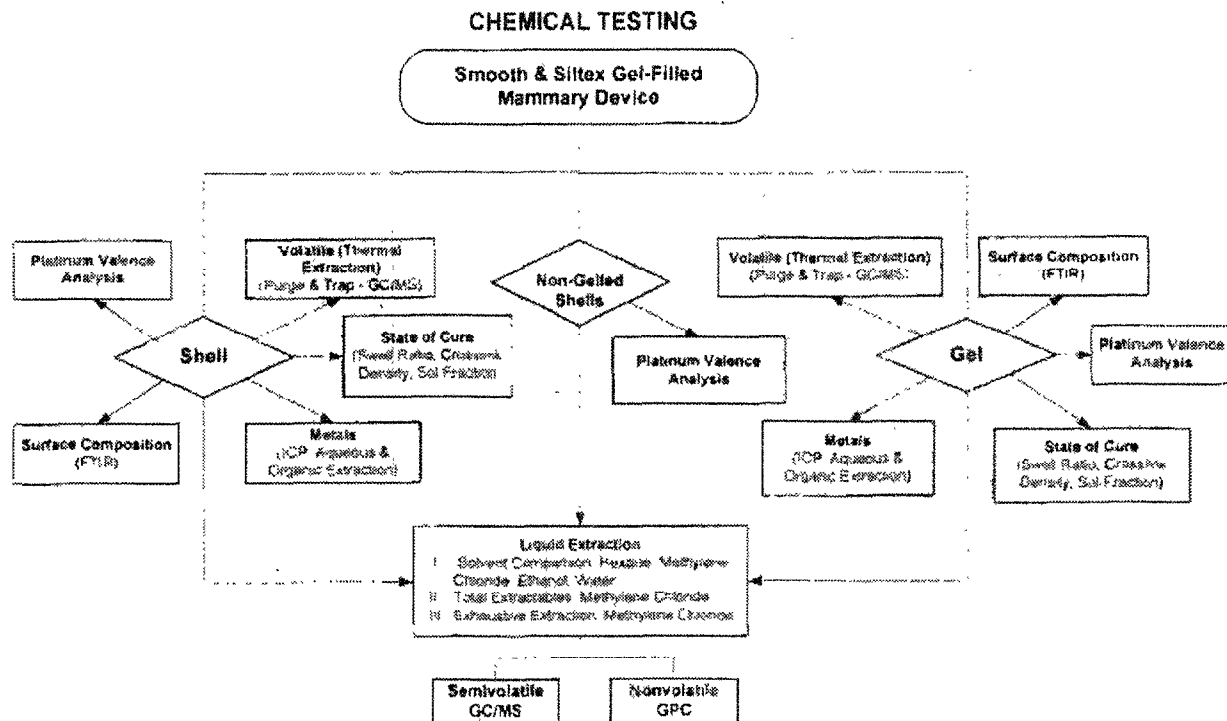


Figure 2-1. Device Testing Scheme

3.0 DEVICE DESCRIPTION AND RAW MATERIALS

Mentor's silicone gel-filled mammary prostheses come in three different variations in order to fit individual patient needs. The Moderate Profile Gel product line is available in both smooth and textured round styles and offers a moderate amount of projection. This product works well for patients who have a wider chest wall and is a good choice for most body types. It is currently the most commonly used of these products.

The Moderate **Plus** Gel (available in both smooth and textured round styles) is intended for patients who require more projection and a slightly more narrow base width. This product is an in-between choice if the Moderate Profile Gel is too wide for a given patient and the High Profile Gel is too narrow. The degree of projection is in-between the two other products as well.

The High Profile Gel (available in both smooth and textured round styles) is intended for patients with a narrow chest wall who are seeking more projection. This is especially relevant in reconstruction when the doctor is trying to match the opposite (non-reconstructed breast) and needs a certain volume implant to achieve symmetry.

All three Siltex gel-filled product lines utilize the same materials and processes for the shell, textured surface, gel, patch, and other minor components. All three smooth gel-filled product lines utilize the same materials and processes for the shell, gel, patch, and other minor components. The different device shapes are achieved by using differently shaped mandrels to dip the shells. All styles (both smooth and textured) of all product lines in this PMA contain a basic smooth shell as one of its components (see Figures 3-1 and 3-2).

All gel-filled mammary prostheses are sold packaged in double sealed thermoforms each with a Tyvek lid and dry heat sterilized. Devices are shipped to customers in individual boxes.

The table below details the catalog numbers for each style of each product line and provides their range of sizes available:

Catalog Number	Gel-filled Device Style	Size Range
350-7XXXBC	Smooth Moderate Profile	100 - 800cc
354-XXX7	Siltex Moderate Profile	100 - 800cc
350-XXX1BC	Smooth Moderate Plus	100 - 800cc
354-XXX1	Siltex Moderate Plus	100 - 800cc
350-XXX4BC	Smooth High Profile	125 - 800cc
354-4XXX	Siltex High Profile	125 - 800cc

The following list of device raw materials are relevant to the device extractables analysis because some of the raw materials can remain in the finished product and therefore could become extractable materials. Mentor uses the list of raw materials as a source for potential target analyte compounds for the chemical testing.

Table 3-1: GEL-FILLED MAMMARY PROSTHESES RAW MATERIALS

Component	Material Name(s)	Part Number(s)	Manufacturer/ Supplier	Master Access File
[]	[]	400009-001	[]	[]
	[]	400598-001 400601-001	[]	[]
	[]	400596-001	[]	[]
	[]	400519-001 400520-001	[]	[]
	[]	400595-001 400594-001	[]	[]
	[]	400001-001	[]	[]

* - Component only present on Siltex Gel-filled Mammary Prostheses

Table 3-1 (cont.): GEL-FILLED MAMMARY PROSTHESES RAW MATERIALS

Component	Material Name(s)	Part Number(s)	Manufacturer/ Supplier	Master Access File
[]	[]	104226-002	[]	[]
		104226-004		
		104226-005		
		104288-001		
	[]	104227-001	[]	[]
		104289-001		
	[]	102739-001	[]	[]
		102738-001		
	[]	102746-001	[]	[]
		102746-002		
	[]	102800-001	[]	[]
		102801-001		
		102587-001		
		102587-002		

Table 3-1 (cont.): GEL-FILLED MAMMARY PROSTHESES RAW MATERIALS

[illegible]

*** - not present in the finished device, contacts components during manufacturing only

Figure 3-1. Smooth Round Gel-Filled Mammary Implant

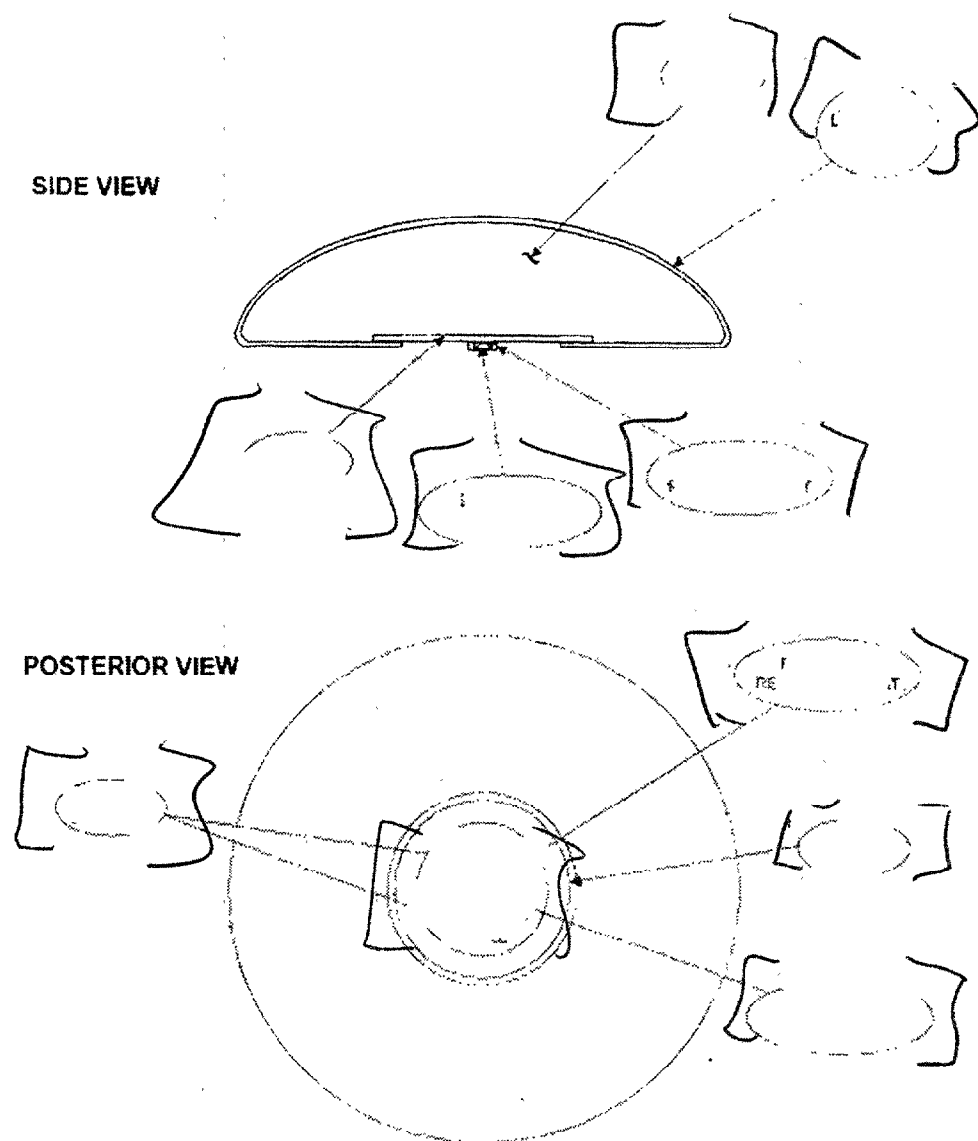
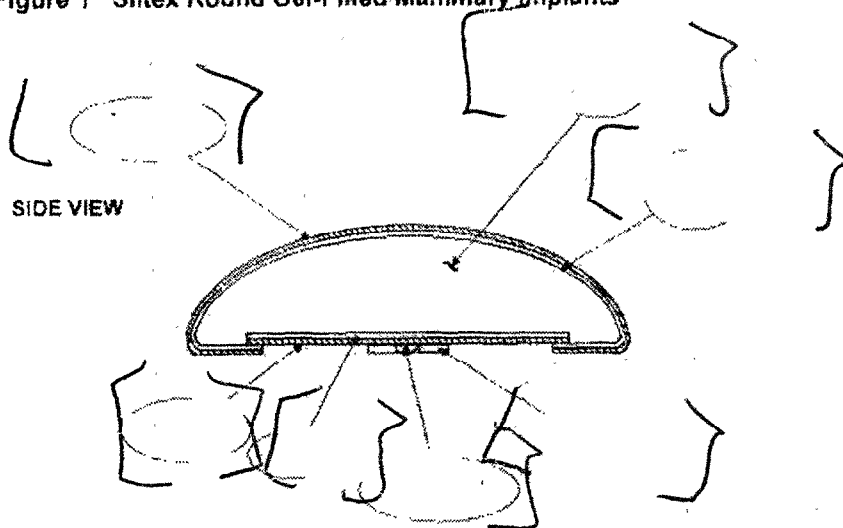
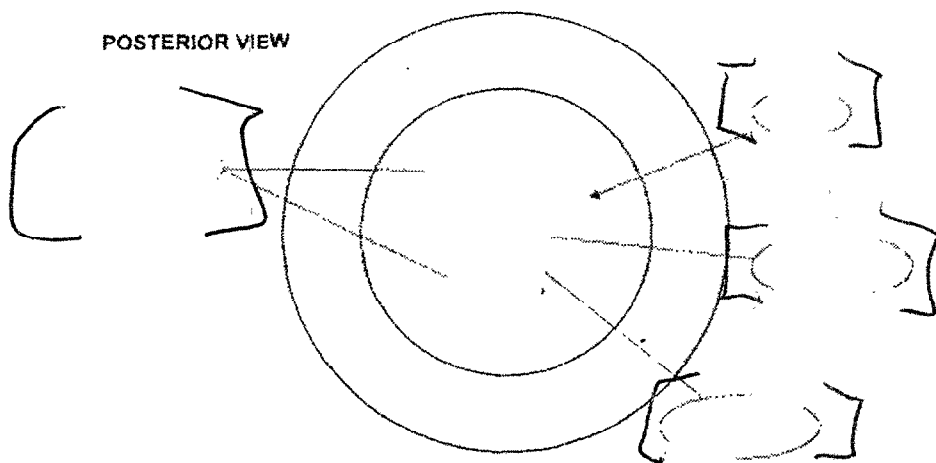


Figure 3-2. Siltex[®] Round Gel-Filled Mammary Implant

Figure 1 Siltex Round Gel-Filled Mammary Implants



POSTERIOR VIEW



4.0 SILICONE CHEMISTRY

4.1 Shell Fabrication (Dipping)

The devices that are the subject of this PMA submission consist of a shell, gel filler, and a patch assembly that seals the patch hole. Textured devices have a layer of roughened elastomer on their exterior surfaces. (See Figure 3-1 and 3-2) All components are fabricated from silicones.

The shells of all gel-filled devices are fabricated in the same manner. Multiple shell layers are produced by repeatedly dipping a mandrel that has the desired shape of the final implant into a dispersion. The bulk of the dispersion solvent (xylene) is evaporated after each layer is applied. The removal of the solvent provides enough physical strength to the last layer so that it is not damaged during the next dip. Two dispersions are utilized in the manufacture of shells for gel-filled devices. One dispersion, Dimethyl Silicone Elastomer Dispersion (FGB-014), yields a poly (dimethyl siloxane) elastomer after curing. The other, ----- Silicone Elastomer Dispersion (FGB-015), yields a poly (----- siloxane) elastomer.

Each dispersion is delivered from the vendor to Mentor as two separate components: Part A and Part B. For the dimethyl dispersion (FGB-014), Part A is a homogeneous solution of vinyl-containing poly (dimethyl siloxane), platinum catalyst and hydrophobized fumed silica (amorphous) in xylene solvent. Part B is a homogeneous solution of poly (dimethyl methyl-hydrogen siloxane) [crosslinker]. The dispersion is provided in two parts to prevent the catalyst from being simultaneously exposed to the unsaturation in the vinyl-containing poly (dimethyl siloxane) and the labile hydrogen of the poly (dimethyl methyl-hydrogen siloxane), the two moieties that react to create crosslinks. If these components were not kept separate, the combination would slowly react at ambient temperatures.

The amorphous silica is a reinforcing filler that increases the physical properties of the final elastomer significantly. The surface of this silica is treated with hexamethyl disilazane (HMDZ). This is done to convert the surface of the silica from hydrophilic to hydrophobic. This conversion causes the silica to perform significantly better as a reinforcing agent, thereby increasing the physical strength of the shell. HMDZ reacts with the silanol groups on the surface of the filler as shown in Figure 4-1. The highly polar silanol surface groups are replaced with the trimethyl siloxane group that is non-polar (hydrophobic).

The two parts of the dispersion are mixed prior to dipping. The combination of the amorphous silica filler and the polymers comprises ----- weight percent of the combined mixture as received from the vendor. Additional solvent may be added to the formulation to adjust its viscosity for dipping.

The ----- dispersion (FGB-015) is precisely the same as the dimethyl dispersion except ----- vinyl-containing poly (----- siloxane) is substituted for the vinyl-containing poly (dimethyl siloxane) in Part A. The ----- polymer has an approximate -----

Each shell is layered on the mandrel by first dipping the required number of layers of the dimethyl dispersion as prescribed in the standard operating procedures. The mandrel is then dipped in the ----- . Finally, the mandrel is dipped again for a prescribed number times in the dimethyl dispersion. The bulk of the xylene solvent is evaporated from each layer under controlled temperature and humidity conditions before the next layer is applied. The shell is then exposed to an elevated temperature for a prescribed amount of time to cure the shell to a tough elastomer. Figure 4-2 provides a key to the nomenclature used in chemical equations. These notations are commonly used in describing silicone chemistry. Figure 4-3 shows the general equations for hydrosilylation curing. Figures 4-4 and 4-5 depict the reactions involved in the curing process.

The layer of ----- polysiloxane provides a barrier against the molecular diffusion of filler components through the shell. The diphenyl substituents on the polymer chain effectively impede the movement of all polysiloxanes and modified polysiloxanes through the shell.

In both dispersions used in the fabrication of shells the amounts of vinyl and hydride -----

essentially all polymers are chemically crosslinked thus minimizing the extractable material in the shell.

4.2 Texturing Shells

The cured shell is removed from the mandrel by cutting a circular section out of the base (manufacturing port) and stretching the shell to remove it from the mandrel. The shells are then soaked in isopropyl alcohol and subsequently dried. This procedure significantly reduces the quantity of extractable compounds (dimethyl and diphenyl siloxanes) in the shell. For smooth devices the shell immediately proceeds to the patch addition step. For textured devices the shell requires additional fabrication steps to add the roughened surface.

addition of the patch to close the patch hole.

The poly (dimethyl siloxane) sheeting that is used to texture shells is a two-part, platinum catalyzed addition-cure system ----- . Both parts are received as solid ingots. Part A consists of vinyl-containing poly (dimethyl siloxane),

-----, platinum catalyst and amorphous silica amorphous silica reinforcing filler. Part B consists of the same three polymers as in Part A plus poly (dimethyl methyl-hydrogen siloxane) and amorphous silica reinforcing filler.

----- reactions involved in the curing of the material to an elastomer are shown in Figure 4-6. The result of this molecular chemistry combined with filler loading and ultimate crosslink density is to produce elastomers that possess high tensile strength. As with the reactive polymer in the dipping dispersions, the molar concentration of the labile hydrogen moiety is carefully controlled relative to that of the vinyl. ----- e ----- . This assures that minimal amounts of uncrosslinked polymers are left that can be extracted from the textured surface. The silanol containing polymers are added to the formulation to convert the surface of the fumed silica from hydrophilic to hydrophobic. This increases the wettability of the silica surface in the mixture which in turn results in improved reinforcement (tensile properties) of the cured elastomer.

4.3 Fabrication and Attachment of Patch to Shell

The next step in the production of a gel-filled device is to add a patch to the shell to close the patch hole. ----- is used to produce patches for all gel-filled devices. Note that these are the same materials that are used to produce the surface on textured devices. This material is processed as described above to produce sheets of uncured material of a prescribed thickness. Some of these sheets of uncured material are cured to an elastomer; i.e., uncured sheets are placed onto the cured sheets to form a laminate. Discs of a prescribed diameter are cut from the laminate sheets. A disc with a much smaller diameter is cut from a sheet of uncured SiTech ----- or NuSil ----- . This small disc is placed on top of the uncured layer of the patch laminate structure. This patch assembly is placed inside a shell with the cured side of the laminate toward the inside of the shell. The patch assembly is positioned such that the outer, uncured surface of the patch contacts the inside of the shell completely around the patch hole. The shell and patch assembly are pressed firmly together in a vulcanization press. For smooth devices, the shell-patch assembly is then subjected to an elevated temperature in the vulcanization press. These conditions cure the polymer layer of the patch and create a bond between the shell and patch. The shell with the attached patch is then post-cured at an elevated temperature.

The procedure for producing the patch for textured devices varies slightly from that for smooth devices as described above. The process is identical to the point at which the laminate structure has been assembled. The patch is positioned inside a textured shell as was done for the smooth shell. In a manner similar to producing a textured shell, polyurethane foam is placed on the uncured side of the patch assembly, and a press is utilized to imprint the contour of the foam onto the uncured polymer. No heat is applied to the patch/shell assembly at this point. The foam is removed from the surface, and the shell/patch is cured at an elevated temperature.

4.4 Laser Marking, Gel-Fill and Curing to Final Gel

The remaining procedures to complete fabrication of devices are the same for both smooth and textured devices. A laser is used to etch the Mentor identification, volume of device and manufacturing lot number on the patch for device traceability. Next, a needle is inserted through the patch and the shell is filled to a prescribed volume with uncured polysiloxane gel.

Once the gel filling is complete, the injection hole is closed with a dispersion coating (one or two drops) consisting of room temperature vulcanizable (RTV) uncured elastomer ----- . The RTV formulation consists of -----

----- -- The chemical transformations of this ----- RTV system have been described in the literature.¹ These transformations are catalyzed by a tin complex and proceed as follows:

- -----

- -----

- -----

The curing mechanism for the formulation is shown in Figure 4-7. A prescribed time is allowed for the RTV material to cure to form a solid bond with the patch. This guarantees that the low viscosity uncured gel cannot leak from the shell prior to or during the gel curing process.

The shell containing the gel precursor formulation is placed in an oven at an elevated temperature. This gel-curing step completes the fabrication of the device prior to packaging, sterilization, etc.

The uncured gel is a two-part, platinum-catalyzed formulation. Part A consists of the platinum catalyst, vinyl-containing poly (dimethyl siloxane) [vinyl polymer] and poly (dimethyl siloxane) [silicone polymer]. Part B consists of vinyl-containing poly (dimethyl siloxane), poly (dimethyl siloxane) and poly (dimethyl methyl-hydrogen siloxane) (methyl-hydrogen or "crosslinker"). Parts A and B are combined prior to

¹ -----

injection into the device shell. The viscosity of the resulting mixture is low. The dimethyl siloxane silicone fluid comprises approximately 50 weight percent of the total formulation. It has a viscosity of approximately 1,000 cps at 25°C. All of the polymers in this formulation are stripped extensively under heat and vacuum to minimize low molecular weight species. This operation minimizes the amount of low molecular weight cyclic dimethyl siloxanes, for example, D4 and its higher homologues, and low molecular weight linear dimethyl siloxanes, for example MD_xM and its higher molecular weight homologues, present in the formulation.

Crosslinking occurs through the addition reaction of the vinyl groups in the methyl-vinyl polymer and the labile hydrogen in the methyl-hydrogen polymer. The silicone poly (dimethyl siloxane) contains no reactive groups and, therefore, does not participate in the chemical reaction. The labile hydrogen is the stoichiometrically limiting reactant in the crosslinking reaction. The formulation contains an excess of vinyl fluid beyond that required to react with the labile hydrogen contained in the methyl-hydrogen polymer. This environment that is dominated by unsaturated materials assures that the platinum catalyst is present as a stable mononuclear platinum-vinyl complex. The platinum in all of the platinum catalyzed addition reactions, whether in a chemical environment of excess silicon-vinyl or excess silicon-hydride, is present in the zero oxidation state upon completion of the curing reaction.² The reaction mechanism involved in the curing of the gel precursor is shown in Figure 4-8.

4.5 Conclusions

Based upon an assessment of the chemistry described in this section, conclusions can be drawn about what chemical compounds, metal compounds and complexes, etc. are present in the finished product and at what concentration. This analysis offers a guide for the analytical work to determine the concentrations of specific materials in the device and a check on the validity of results. Figure 4-9 presents a summary of the reactants, processing materials, catalysts, additives, etc. that are utilized in the fabrication of the devices that are the subject of this submission.

4.5.1 Shell

The molar quantities of the vinyl and labile hydrogen moieties are controlled in the shell polymer dispersion formulations ----- relative to the molar vinyl content. This assures that essentially all of the material is crosslinked, which, in turn, results in very low amounts of uncrosslinked material that can be extracted from fabricated shells, even with aggressive solvents. Analytical data bear this out since total extractables were measured to be approximately 1.5-2.0 weight % of the shell.

Platinum is present in the fabricated shells at very low concentrations. It has been established many years ago by detailed analytical work as referenced above that

² J. Stein *et al.*, "In Situ Determination of the Active Catalyst in Hydrosilylation Reactions Using Highly Reactive Pt(0) Catalyst Precursors", Journal of the American Chemical Society, 1999, Volume 121, pp 3693-3703.

in the reaction environment presented in the fabrication of shells, the platinum will be in the zero oxidation state at the completion of the curing reactions.

Amorphous silica is used as a reinforcing filler in the shell formulation. The mild processing conditions for fabrication of shells will not convert amorphous to crystalline silica. This thermodynamic transition would require temperatures in excess of 700°C.

Due to the polarity difference provided by the bulky -----l units on the chains, ----- modification of polymer in one layer of the shell severely inhibits the diffusion ("bleed") of low molecular weight siloxanes (e. g., D₄, D₅, etc.) through the shell. The ----- of the total polymer in the ----- layer of the shell. After shells are removed from dipping mandrels, they are subjected to an isopropyl alcohol soak. This process significantly reduces low molecular weight ----- siloxane species in the shells.

4.5.2 Texture and Patch

As with the shell dispersion formulations, the formulations for the sheeting from which texturing and the patch are fabricated are carefully balanced to assure that essentially all of the vinyl and labile hydrogen are reacted with one another. The same conclusions can be reached for these components as for the shell; i.e., the extractable materials will be low. Amorphous silica reinforcing filler is included in the formulations and, due to the mild processing conditions relative to those required to convert the silica to a crystalline form, the amorphous silica will remain in that state.³ No ----- the by-product of the reaction of the crosslinker with ambient moisture, was detected in the extracts from the device. The combined formulation, Parts A and B, of the patch and texturing material contains very low concentration of platinum. No unusual compounds were detected from the area on the patch that was exposed to laser etching.

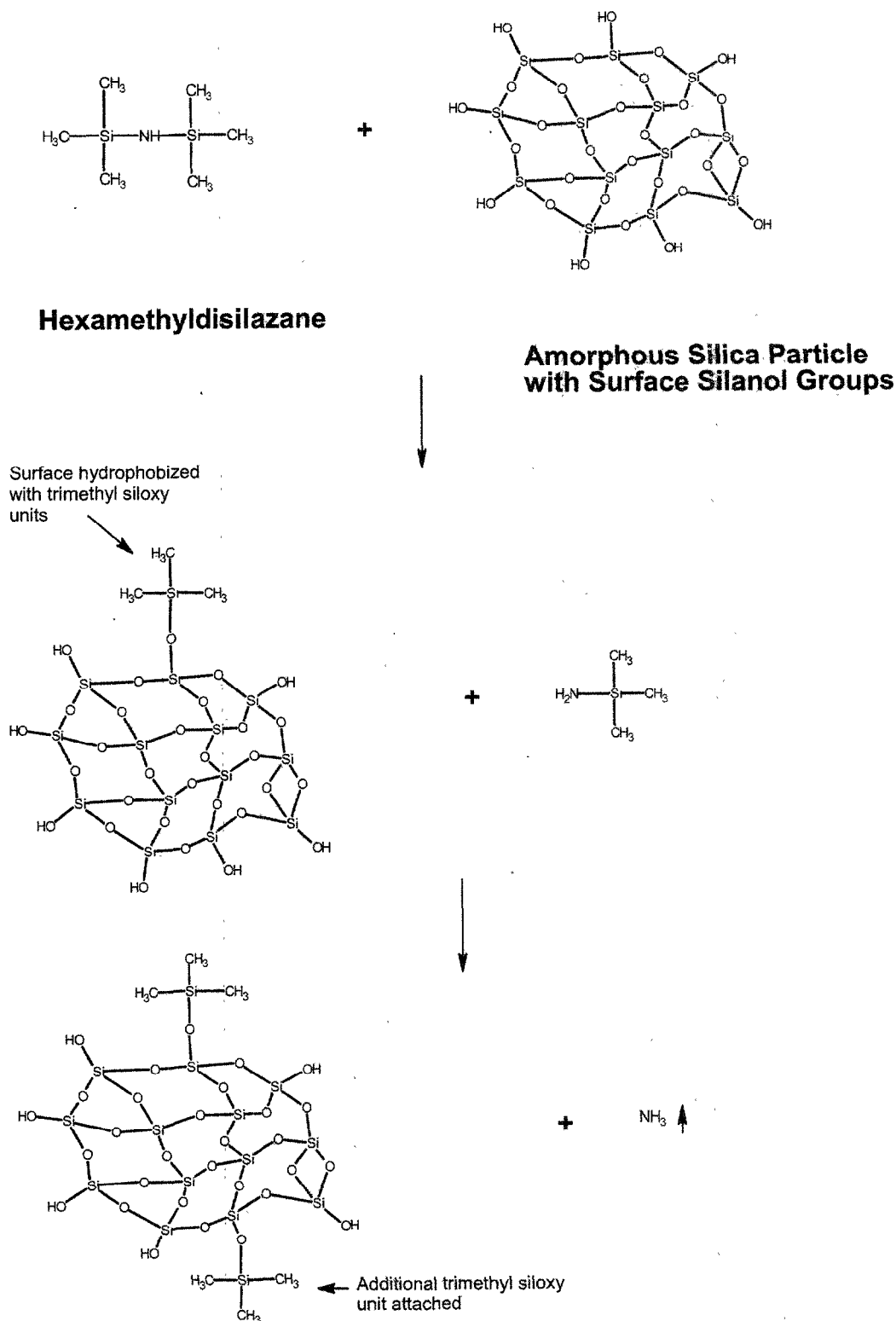
4.5.3 Gel

The amount of the vinyl-containing polymer significantly exceeds the stoichiometric requirement of the labile hydrogen in the gel formulation. This creates the lightly crosslinked molecular structure required to form a gel. This lightly crosslinked structure is embedded in unreacted materials to produce the desired gel consistency. This is typical of silicone gels. The molar ratio of vinyl to labile hydrogen means that there will be a significant excess of vinyl-containing compounds in the cured gel. The formulation contains approximately

³ NIOSH Method 7501 for Amorphous Silica. Standard Procedures. "Method 7501 uses the property that most amorphous forms of silica will convert to cristobalite with heat treatment. The x-ray analysis steps are similar to Method 7500, but the sample is ashed and fired to 1100 or 1500°C depending on the type of amorphous silica suspected prior to final transfer to the silver filter. The sample is then analyzed for cristobalite." <http://osha.gov/SLTC/silicacrystalline/smithdk/standard.html>

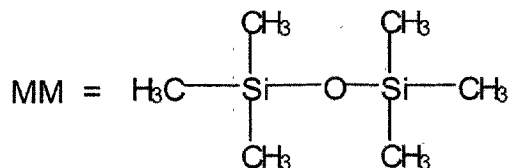
----- silicone oil poly (dimethyl siloxane) that does not participate in the curing reaction. All of the siloxane polymers in the gel formulation are intensively stripped under heat and vacuum to remove low molecular weight species, cyclics, such as, D₃, D₄, D₅, D₆, etc. and linears, such as, MDM, MD₂M, MD₃M, etc. Analytical results confirm the low concentrations of the low molecular weight extractable materials from these devices. Very low levels of platinum are present in the final, cured gel.

Figure 4-1. Reaction of Hexamethyldisilazane with Surface Silanol Units

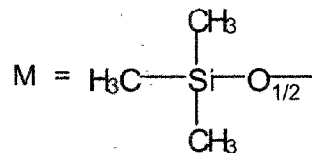


The trimethyl siloxy units on the surface shield adjacent surface silanol groups so that they cannot react (become hydrophobized). Therefore, the surface can be only partially covered with trimethyl siloxy units.

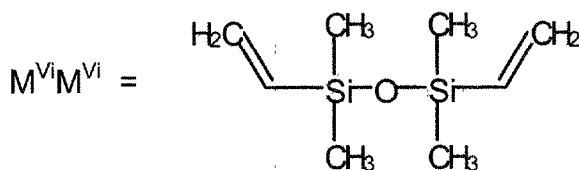
Figure 4-2. Key to Nomenclature Used in Chemical Equations



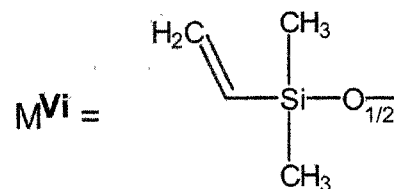
Trimethyl Disiloxane Endblocker



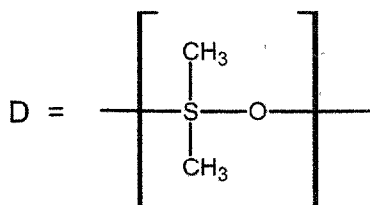
Trimethyl Siloxy



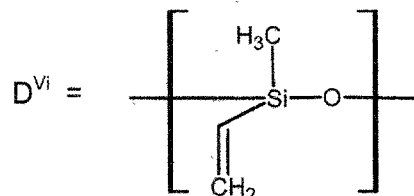
Dimethyl Vinyl Disiloxane Endblocker



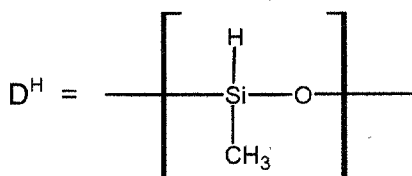
Dimethyl Vinyl Siloxy



Dimethyl Siloxane



Methyl-Vinyl Siloxane



Methyl-Hydrogen Siloxane

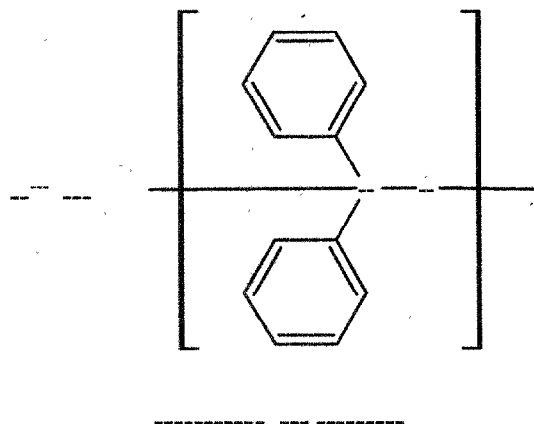
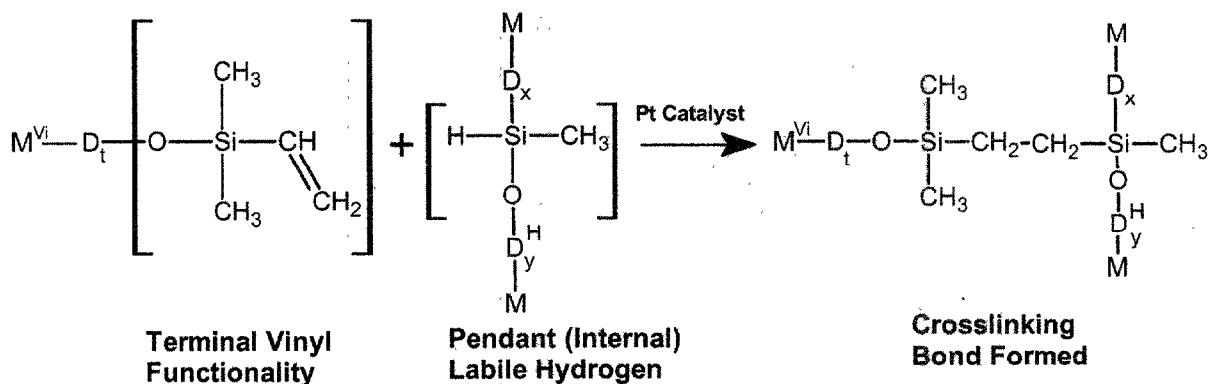
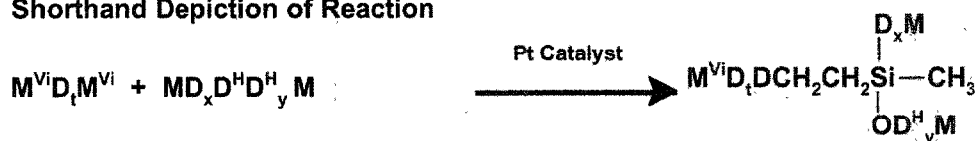


Figure 4-3. Hydrosilylation Mechanism (Addition Reaction)

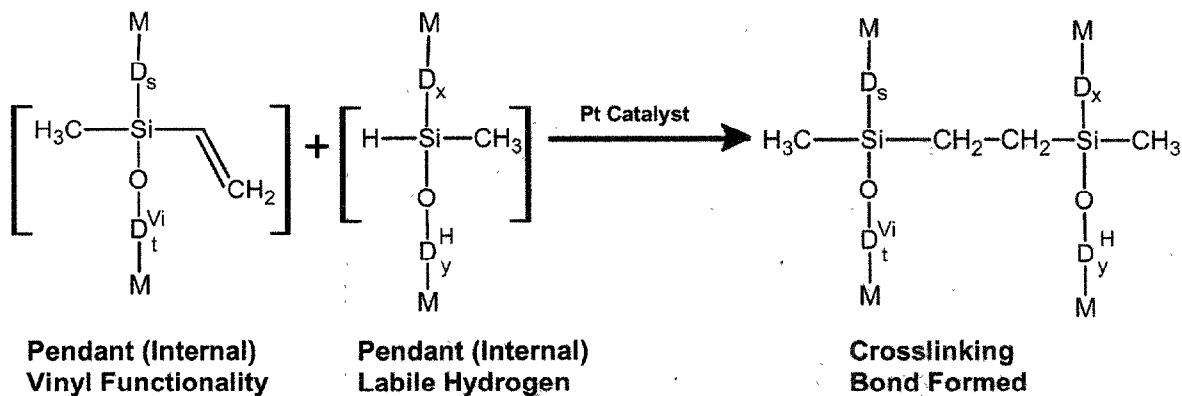
Mechanism for Terminal Vinyl Functionality



Shorthand Depiction of Reaction



Mechanism for Internal (Pendant) Vinyl Functionality



Shorthand Depiction of Reaction

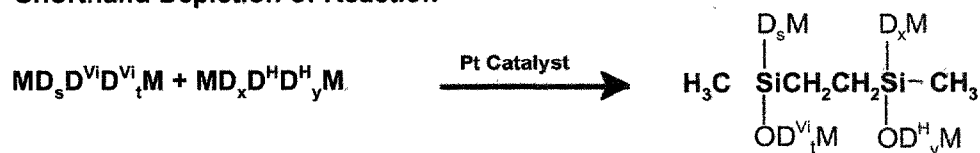


Figure 4-4. Chemistry of Shell Dimethyl Layer Cure

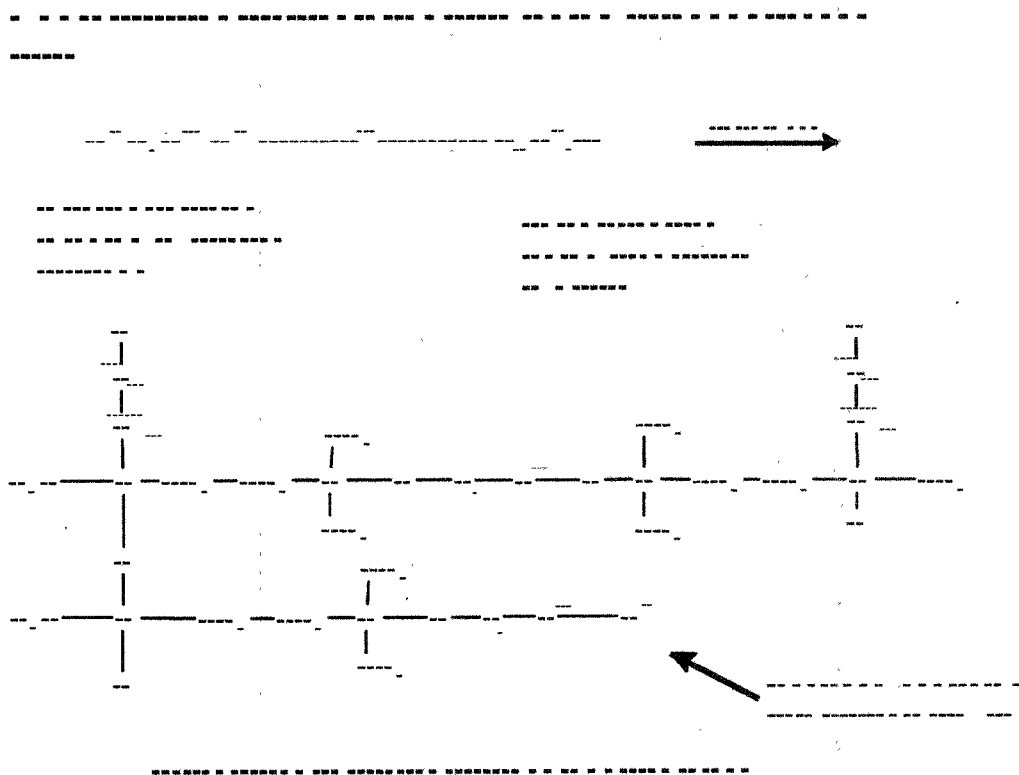
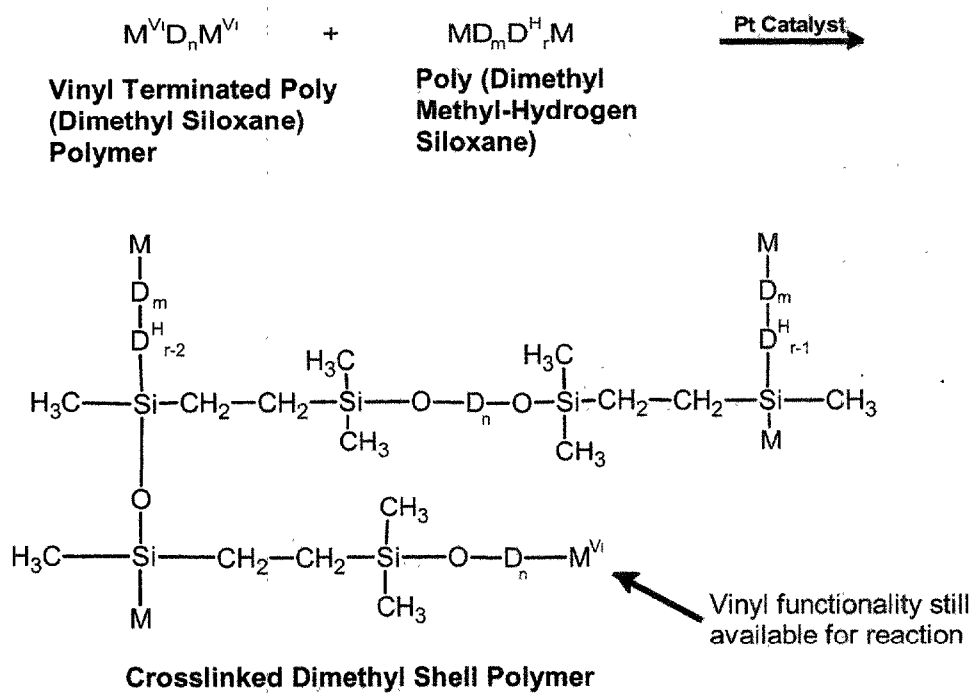


Figure 4-6. Chemistry of Texturing and Patch Cure

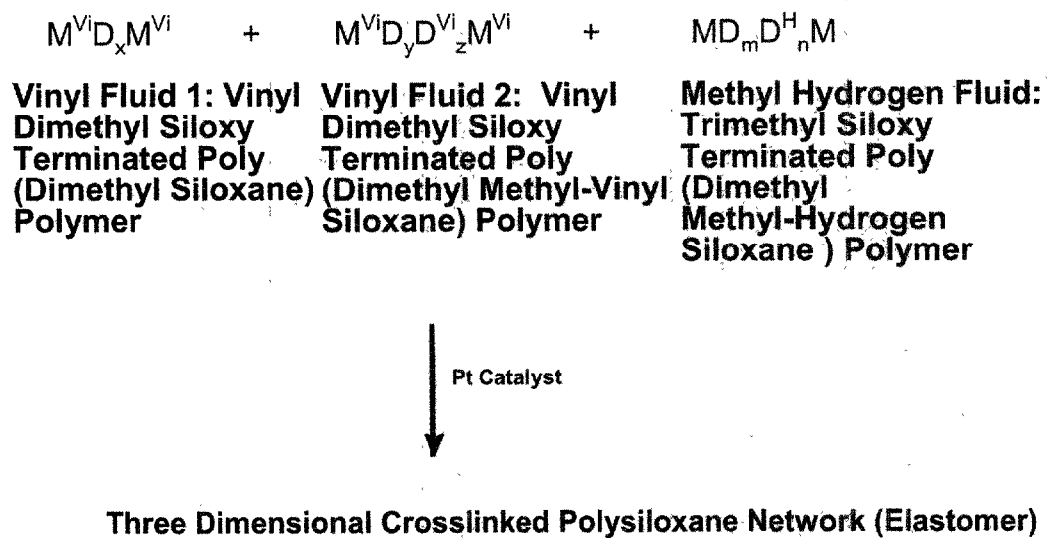
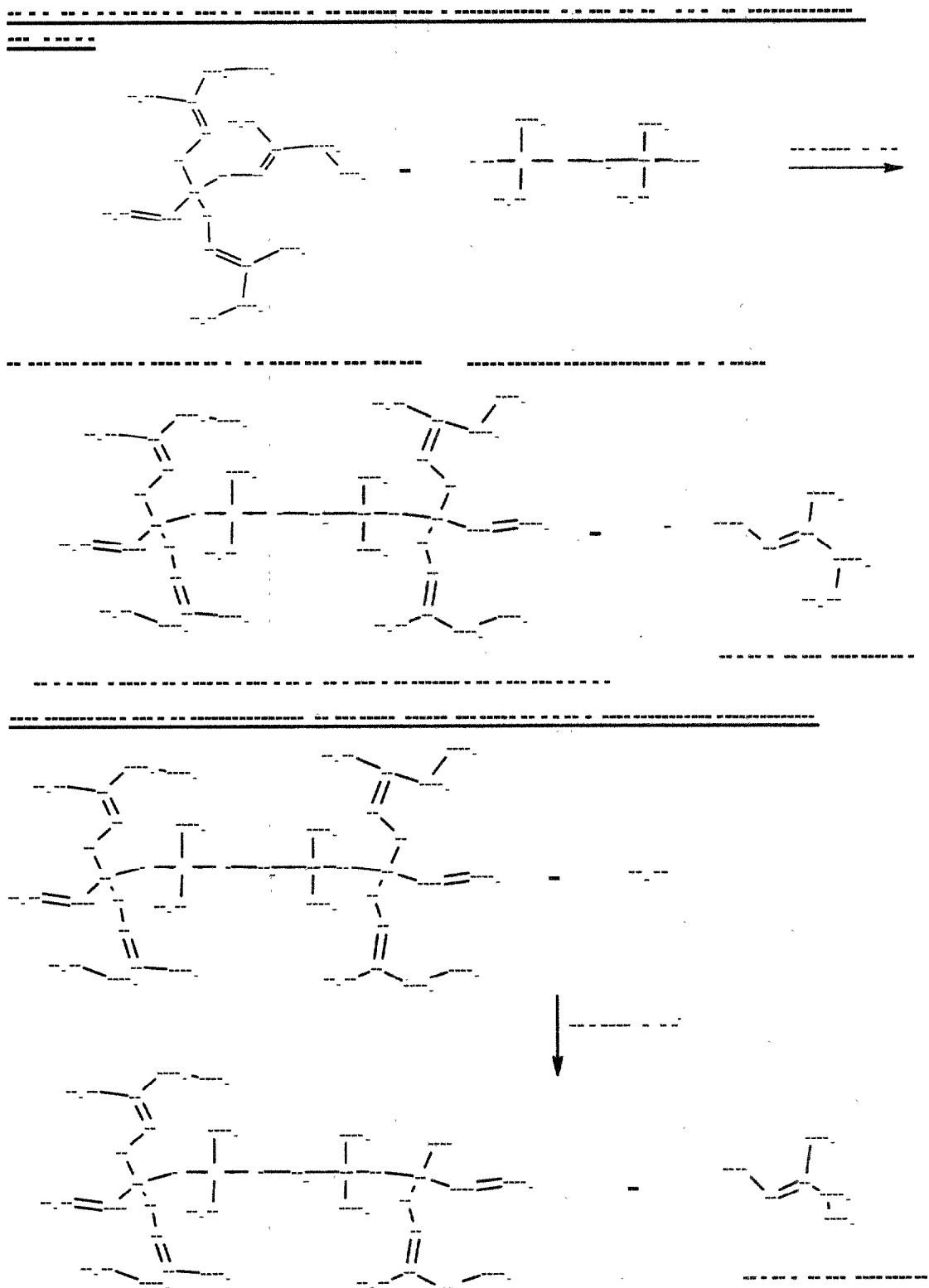


Figure 4-7. Chemistry of Cure of RTV Dispersion Sealant for Hole Left by Gel Precursor Injection Needle



**Figure 4-7. (Continued) Chemistry of Cure of RTV Dispersion Sealant
for Hole Left by Gel Precursor Injection Needle**

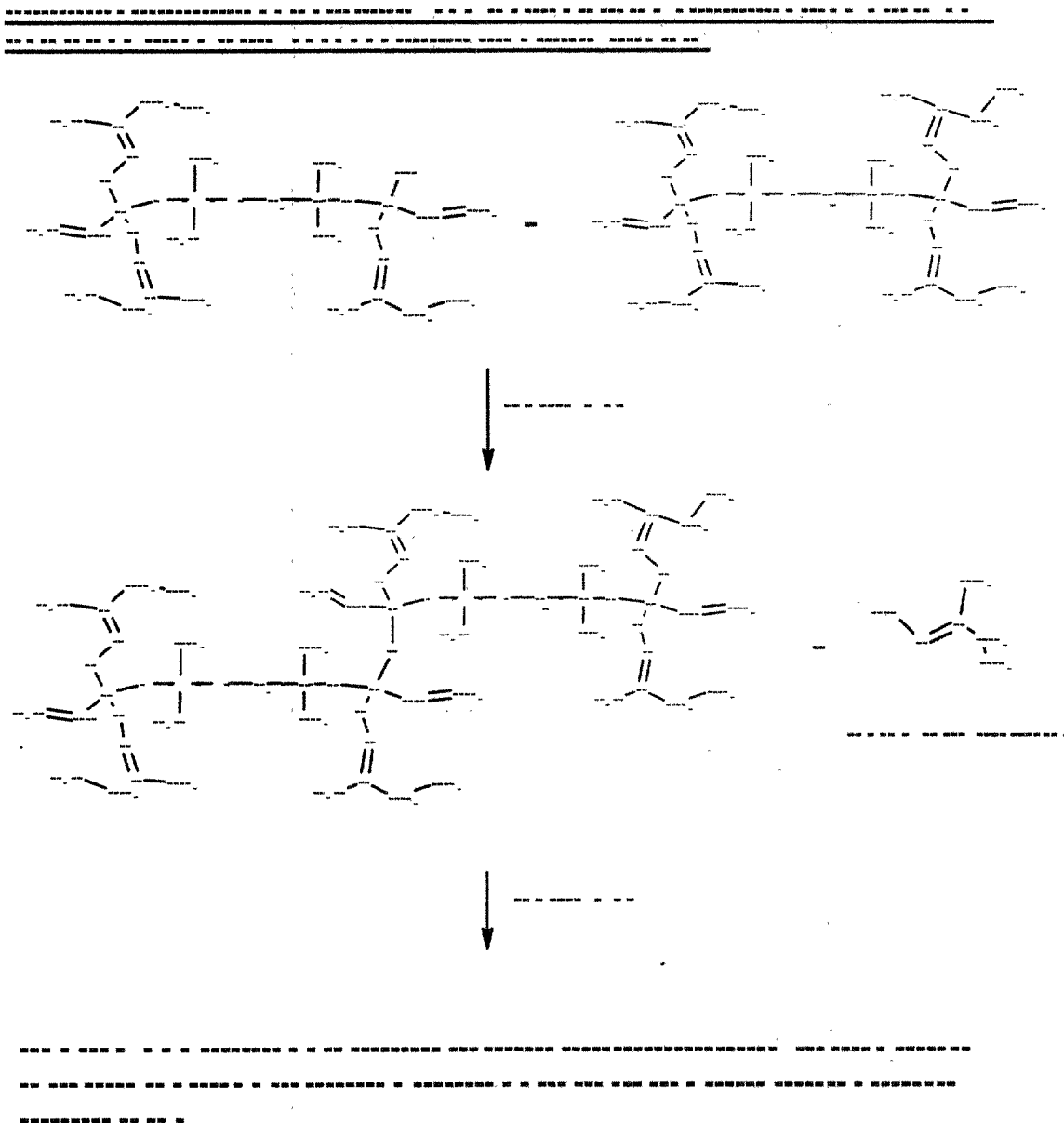


Figure 4-8. Chemistry of Gel Curing

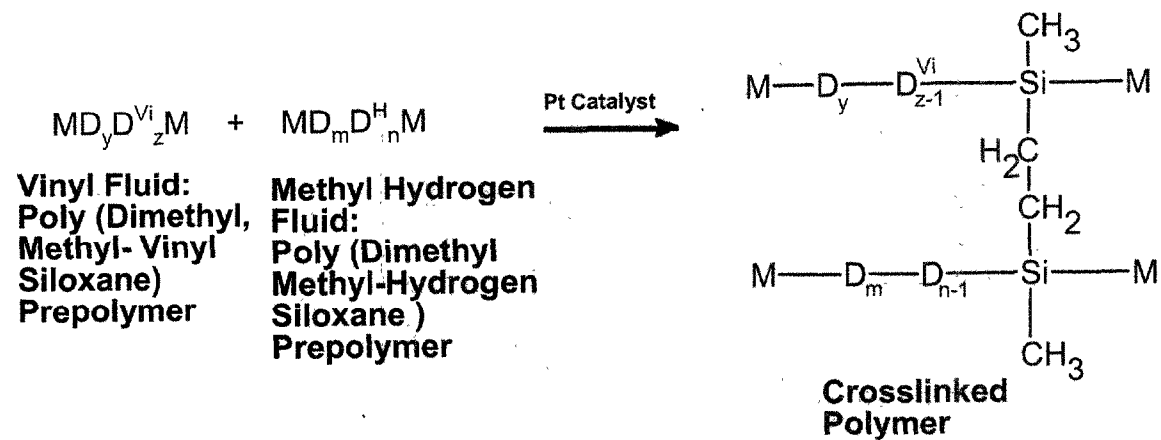


Figure 4-9. Potential Candidates for Analytical Quantification Based Upon Chemistry

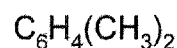
Vinyl terminated oligomer or
Dimethyl-vinyl siloxane terminated poly (dimethyl siloxane)



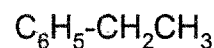
Crosslinker, Silicon Hydride Fluid or
Oligomer Containing Silicon Hydride or
Trimethyl siloxane terminated poly (dimethyl, methyl-hydrogen
siloxane)



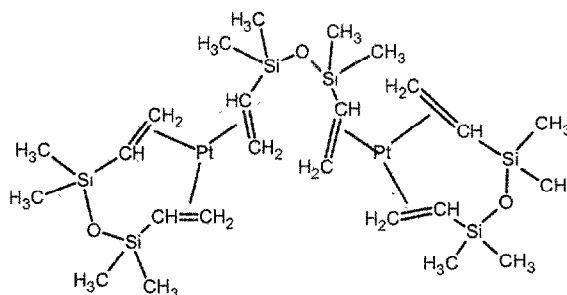
Xylene or Dimethylbenzene



Ethyl benzene



Platinum catalyst, Chloroplatinic Acid
Coordinated with Vinyl Compounds,
Karstedt Catalyst



Amorphous Silica Reinforcing Filler, Silicon Dioxide



Hexamethyldisilazane or HMDZ



Methyl-vinyl oligomer or fluid
Trimethyl siloxane terminated poly (dimethyl, methyl-vinyl
polysiloxane)

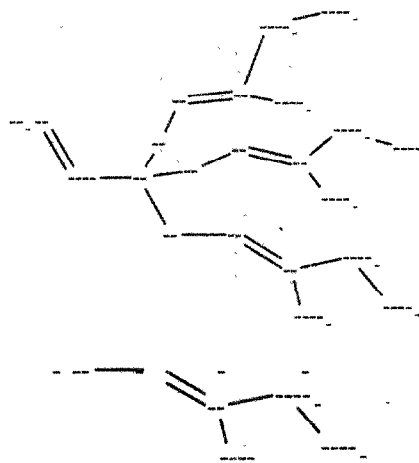


Silanol fluid, Dimethyl silanol fluid or
Dimethyl silanol siloxane poly (dimethyl siloxane) oligomer



Figure 4-9. Potential Candidates for Analytical Quantification Based Upon Chemistry (Continued)

Tin catalyst or
Dibutyltindilaurate



5.0 CHEMICAL ANALYSIS

The materials of construction, processing chemicals and materials, tooling that contacts the devices during fabrication and packaging for the devices covered by this submission are listed in Table 3-1. The table below presents a summary of the vendors for each component of the gel-filled devices.

Table 5-1. Summary of Vendors for Device Components

Component	Material Name(s)	Manufacturer/ Supplier
Smooth Shell	Dimethyl Silicone Elastomer Dispersion	SiTech, LLC
	"-----" Silicone Elastomer Dispersion	SiTech, LLC
Shell Textured Layer, Patch, Patch Fill Reinforcement	----- Silicone Elastomer:	NuSil Silicone Technology
	(OR ALTERNATIVELY) ----- Silicone Elastomer:	SiTech, LLC
Gel	Silicone Gel	SiTech, LLC
Dip Coat Fill	Dispersion Coating 92-009 (Silicone)	Dow Corning/ K.R. Anderson

The testing results that are documented in this section of the Chemical Module are based on devices produced from SiTech LLC raw materials for the two shell dispersions, the texture layer, the patch, the patch fill reinforcement feature and the gel. -----
---- was used to create the "dip coat fill" feature on the devices. Testing results were used to demonstrate the equivalence of products produced with changes in process conditions, process equipment, production tooling, raw materials and addition of a device laser marking step to the manufacturing process. Specifically, the changes encompassed by this PMA product chemical testing data are as follows: (1) reduction in sterilization cycle time from 48 to 35 hours, (2) use of a new calender with chilled rolls for the production of uncured elastomer sheeting that is subsequently used to create the texture layer on devices and patches and patch fill reinforcement components, (3) substitution of Ertalys polyester resin dipping mandrels with ones constructed from Teflon-coated stainless steel, (4) substitution of ----- for -----
----- as precursors for the fabrication of sheeting used in the texturing of devices and for the fabrication of patch and patch fill reinforcement components and (5) laser marking the company name and logo, device volume and manufacturing lot number on device patches. The results in this section of the Chemical Module represent the devices that are the subject of this submission with the exception that only ----- was used for the elastomeric sheeting and ----- was not and only ----- mandrels were used for dipping shells and ----- mandrels were not.

In order to maintain flexibility in raw material availability, Mentor will use either -----
----- or NuSil Silicone Technology ----- as the precursor for the fabrication of the

texture layer (for Siltex[®] devices), the patch and the patch fill reinforcement feature. The equivalence of substituting one material for the other in the production of the devices will be documented later in this Chemical Analysis Section. As background for the demonstration of chemical equivalence that will follow later in this section, it should be noted that the formulation and specifications for all intermediates going into the formulation of the two products are the same. The reason for this is that SiTech licensed the formulation of ----- from NuSil. NuSil originally produced the material for sale to Mentor. SiTech qualified the processing equipment and process for producing ----- Only production locations and equipment vary. Documented chemical evidence will be presented to substantiate the equivalence of the two materials.

The second exception can be seen in Table 3-1 under the heading, "Indirect Manufacturing Materials" in the "Components" column. Mentor will use dipping mandrels made of either ----- or ----- for the fabrication of shells. This choice is to allow flexibility in choice of tooling in order to control manufacturing costs in shell production. A study was conducted to demonstrate device chemical equivalence⁴. This report is discussed in Section 5.9.

The 35-hour sterilization cycle was demonstrated to achieve sterile product. The new calender and mandrel changes were qualified in manufacturing to demonstrate that in-process sheeting and shells and final product produced from them meet all specifications and validation requirements. Likewise, the addition of laser marking of the patch to the manufacturing process was qualified with regard to potential effects on finished device physical properties. The qualification validated the use of this marking technique. A separate chemical characterization study was conducted to demonstrate that this added manufacturing step did not produce any new compounds in the finished device.⁵ The results of this report are discussed later in this section. All process qualifications and validations and the chemical characterizations discussed in this submission were successfully completed prior to the implementation of each in the sale of finished devices with any of these changes.

Please note that in this chemical analysis module, one version of chemical terminology structures is used while in the source reports (CP # report) a different version is used. The following details the differences:

⁴ Wenkai Ma, Grace Chiang, Project Report Number CP 333, *Total and Semivolatile Extractables Analyses of Gel-Filled Mammary Prostheses: Teflon/Stainless Steel Shell Mandrel Qualification*. December 19, 2001.

⁵ G. M. Allen, Report Number CP 353, "Chemical Testing of Laser Marked Patches for Mammary Implants", November 27, 2002.

Generic Compound(s)	Chemistry Module Terminology	CP Report Terminology
Vinyl terminated oligomer or dimethyl-vinyl siloxane terminated poly (dimethylsiloxane)	$M^{Vi}D_mM^{Vi}$	VD_m
Cyclic -----	--- ---	-- --
Cyclic dimethyl -----	--- --- --- --- --- ---	-- -- -- -- -- --

5.1 Volatile Components

Volatile components were determined by a dynamic headspace purge/trap concentrator coupled with a gas chromatograph/mass spectrometer instrument. This analytical procedure consists of two steps: (1) a sample elution and adsorption step followed by (2) a desorption analysis with GC/MS. Specifically, low molecular weight compounds on the surface of a sample are volatilized and carried by a stream of helium to a porous adsorbing material where they are adsorbed. Total duration of the purge/trap cycle was 15 minutes. The sample temperature was held at 60°C during this step. Temperature effect during the purge/trap step was determined by running tests at lower (50°C) and higher (70°C) temperatures. Based upon the results of these tests, 60°C was chosen as acceptable. Upon completion of the purge collection step, the trapped volatiles were thermally desorbed from the adsorbent and sampled to a gas chromatograph/mass spectrometer for identification and quantification.⁶

The results of Report CP 358 demonstrated that exhaustiveness was achieved with the first purge for all compounds in the samples as well as in matrix blank spikes. There were either none or only residual quantities (at background levels) of the analytes collected in subsequent purges. This is because the levels of all analytes were low. Thus exhaustiveness was demonstrated for the purge/trap technique when applied to the test samples.

⁶ Grace H. Chiang, Report Number CP 358, *Volatile Extractables Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, January 28, 2003.

The quality checks for a complete method validation included instrument checks and validation, determination of detection limits, demonstration of linearity of standard calibration curves, demonstration of method reproducibility, verification of recovery of matrix spikes and verification of the effectiveness of the purge/trap technique for volatiles collection.

Compound identification for unknown peaks was achieved by mass spectra matching against reference spectra and retention indices values. Volatile compounds were those with retention index of less than 1200 (equivalent to n-dodecane).

Quantification of identified compounds was based upon calibrations with known standards (internal and external). For compounds for which standards were not available, quantification was performed using the response factor based upon either the nearest homologue or internal standard.

Target analytes for the volatiles analysis were the following:

Manufacturing Process Solvent Residues -

- Isopropanol
- Toluene
- Xylenes (ethylbenzene and o-, m-, p-xylenes)
- Cyclohexanone
- Normal alkanes (C₇-C₁₂)

Materials from Implant Components -

- Linear polydimethylsiloxanes: MM through MD₂M
- Cyclic Dimethylsiloxanes: D₃-D₅
- 1-ethynyl-1-cyclohexanol (ECH) (Polymerization inhibitor used to prevent curing of elastomers prematurely, such as, in storage. None was detected in any of the samples.)

Typical detection limits for target analytes was approximately 1 µg/g or less. Detection limits for isopropanol and ECH were 0.8 and <1.1 µg/g, respectively. Samples were run in triplicate. Recoveries were generally in the range of 100% ± 20%.

Siltex Round Moderate Profile Gel-Filled implants were chosen as representative of the devices that are the subject of this submission because not only do they represent the Siltex Gel-filled implant, but the textured shell is a smooth shell (the same used with Smooth Gel-filled implants) covered with a textured layer.

5.1.1 Shell

Shell samples were prepared by first removing the bulk gel filler from the shell. Trace amounts of gel were removed from the shells by wiping with lint-free sheets of cleaning material. Shells were cut into 2mm x 2mm pieces and 0.2 g of the pieces were sampled. In addition, non-gelled shells (i.e., shells which had

been processed using all manufacturing steps except that no gel ever contacted the shell) were analyzed.

There were 11.1 $\mu\text{g/g}$ volatiles present in non-gelled shells. The shell from finished devices contained 10.2 $\mu\text{g/g}$ volatiles. Isopropanol, silanes and most of the common solvents or solvent impurities were only found in the shells. Refer to Table 5-2 for a detailed tabulation of data from the volatiles analysis.

5.1.2 Gel Filler

The gel filler was removed from the shell. A gel sample of approximately 0.1 g was taken from the gel filler.

The gel filler contained 2.8 $\mu\text{g/g}$ volatiles. Cyclic dimethyl siloxanes accounted for about 80 weight % of the total volatiles from the gel filler. No trace quantities of other target analytes were detected in the gel. The remaining 20% of the volatiles were low levels (i.e., hundreds of part per billion or less) of a few miscellaneous compounds. Refer to Table 5-2 for a detailed tabulation of data from the volatiles analysis.

5.1.3 Whole Device

By combining the results of the shell and gel analyses, taking into account the weight of each compared to the total device weight, the quantity of the various component compounds can be calculated on a whole device basis. On a whole device basis, the Siltex Round Moderate Profile gel-filled mammary implant contained a total of 3.7 $\mu\text{g/g}$ volatile substances, of which approximately 60% were dimethylsiloxanes ($\text{D}_3\text{-D}_5$). The remaining minute quantities ($< 1.6 \mu\text{g/g}$) of detected compounds were solvents, solvent impurities, or miscellaneous silicone related compounds. Table 5-2 lists the volatile compounds found in the components and whole device and their respective quantities.

5.1.4 Conclusions

The volatile compounds detected by the purge/trap sampling technique coupled with GC/MS analysis are at very low concentration in the non-gelled shells and shells and gel from finished devices. Finished device samples contained approximately 3 and 10 $\mu\text{g/g}$ for the gel and shell, respectively. For the gel, approximately 2.3 $\mu\text{g/g}$, or approximately 82 weight %, of the volatiles was cyclic dimethylsiloxanes. Approximately 4.8 $\mu\text{g/g}$, or approximately 50 weight %, of the volatiles detected in finished shells were cyclic siloxanes and other silicon-containing compounds. The remainder of the volatiles in the shell is trace quantities of solvent residues.

Table 5-2. Volatile Compounds in Siltex Round Moderate Profile Gel-Filled Mammary Implants (SiTech Texture Layer, Shell and Gel Filler)

Compound	Nongelled Shell	Gel Filler (A)*	Shell (B)*	Whole Device (C)*
Device Traceability (Cat. No./Lot No./Size)	NA/ 2511121/ 100cc	354-1007/ 251121/100cc		
	ug/g			
Cyclic Dimethyl Siloxanes				
D3 ¹	NA	0.18	0.19	0.18
D4 ¹	<0.06	0.49	0.23	0.46
D5 ¹	0.28	1.60	0.79	1.47
Miscellaneous Silicon-Containing Compounds				
Methoxytrimethylsilane ²	3.13	ND	3.34	0.43
Dimethoxydimethylsilane ²	NA	NA	0.20	0.03
Methyltriethoxysilane ²	0.04	ND	NA	NA
Tetramethyldiethyldisiloxane ²	ND	0.05	NA	0.04
Miscellaneous Solvent Residues and Others				
Acetone ²	1.02	ND	1.38	0.18
Isopropanol ^{1**}	<1.06	ND	2.03	0.26
2-Pentanone ²	0.05	NA	NA	NA
Methyl Butanoate ²	0.04	0.09	NA	0.08
4-Methyl-3-penten-2-one ²	0.07	ND	0.08	0.01
Ethylbenzene ¹	<0.01	NA	NA	NA
m-&p-Xylenes ¹	0.06	<0.09	0.05	0.08
o-Xylene ¹	<0.02	NA	NA	NA
alpha-Pinene ²	0.02	NA	NA	NA
Cyclohexanone ¹	<0.56	ND	NA	NA
1-Ethyl-2-methylbenzene ²	0.02	ND	0.06	0.01
Decane ¹	0.09	NA	NA	NA
Benzaldehyde ²	0.04	ND	0.08	0.01
1,3,5-Trimethylbenzene ²	0.04	NA	0.04	0.01
Limonene ²	0.02	NA	0.05	0.01
Undecane ¹	1.39	<0.34	<0.45	0.35
Acetophenone ²	0.03	ND	0.06	0.01
Dodecane ¹	3.00	NA	<0.55	0.07
Total Volatiles (ug/g device)	<11.07	<2.84	<10.16	3.67

ND = Not Detected, S/N <3.0

NA = Not Applicable. At least one of the replicates has a ND value

Data preceded with a "<" symbol meaning a less than method detection limit value

* - C = whole device calculation = $(A*99.0144+B*14.4773)/(99.0144+14.4773)$

** Integration based on Extracted Ion Chromatogram.

¹ Measurement based on external and internal standard calibrations.

² Measurement based on the response factor of closest internal standard.

5.2 Extractable Analysis on Shell and Gel from Devices that are the Subject of this PMA Submission

Total solvent extractables were determined by gravimetric analysis. There are two types of extractables which make up total extractables. They are (1) extracted compounds up to approximately 1,500 Dalton molecular weight, and (2) higher molecular weight nonvolatile extractable compounds containing oligomeric and polymeric species.

Extracted compounds up to approximately 1,500 Daltons molecular weight, referred to as "semivolatiles" in the references, were identified and quantified by direct liquid sample injection into a gas chromatograph/mass spectrometer (GC/MS). Higher molecular weight materials containing oligomeric and polymeric species, referred to as nonvolatiles, were analyzed by gel permeation chromatography (GPC) from aliquots of total extractables, for characterization of molecular weight. The GPC method utilizes two separate detector systems: refractive index (RI) and ultraviolet/visible (UV/Vis). The UV/Vis detector responds to ----- modified siloxanes and is insensitive to dimethyl-modified siloxanes. The RI system is sensitive to dimethyl-modified siloxanes and has little response to ----- -modified siloxanes. The combination of these detectors provides an effective means of analyzing samples with a combination of the two types of compounds.

For both the GC/MS and the GPC methods compound identification is accomplished through the comparison of the characteristics of the spectra for the compound to reference libraries of spectra for known compounds. Quantification of the amounts of compounds in complex sample mixtures is accomplished through the use of internal and external, well defined standards.

Total extractables of a device were calculated based on extractables of the shell and gel components separately. For the total extractables from the device, the extractable amounts of each component were combined based upon each components weight fraction of the total device.

Monomers are not used in this silicone system, so there are no residual monomer target analytes. No peroxide curing systems are used in this product so polychlorinated biphenyls (PCB's) were not a target analyte. ----- is used in the manufacturing process of the Mentor Siltex™ textured device. It is a processing aid and is not present in the product, so aromatic amines would not be seen and were not a target analyte.

5.2.1 Total Extractables Analysis

Siltex™ Round Moderate Profile devices (100 cc) were selected as representative of the families of gel-filled implants. The sample population consisted of three devices from the same manufacturing lot. Gel samples were removed from

finished product and subjected to a Soxhlet extraction procedure utilizing methylene chloride as the solvent. The extraction was conducted at a M/V of 1/150 for 30 hours. Upon completion of the Soxhlet extraction, an aliquot of the solvent from the extraction was reserved for semivolatile analysis by GC/MS. The remainder of the extraction sample was then dried at room temperature, desiccated and weighed. Total extractables and recovery were calculated from the various gravimetric determinations. Three gel sample replicates from each device and a method blank were analyzed. The representative finished devices contained a mean average of 73% solvent extractable material. See Table 5-3. The recovery (residue weight/weight loss of original gel sample) was >98%.

Table 5-3. Total Extractables on a Nongelled Shell and Calculated for a Whole Device (SiTech Textured Layer, Shell, and Gel Filler Materials)

Device (Raw Material Vendor)	Weight % Total Extractables	
	Nongelled Device (SiTech)	Regular Gel-Filled Device (SiTech)
Device Traceability (Cat. No/Lot No./Size)	NA/251121/100cc	354-1007/251121/100cc
Shell Assembly	1.86	10.43
Gel Filler	—	82.74
Whole Device	—	72.96

%Total extractable in whole devices = sum (%extractable found in individual component x component wt)/whole device wt

5.2.2 Semivolatiles Analysis

5.2.2.1 Shell

The nongelled shell contained non-detectable amounts of D₄-D₇ and approximately 2700 µg/g total of D₈-D₂₁. It contained no detectable amounts of linear dimethylsiloxanes (MDM-MD₁₇M). No vinyl-modified cyclic dimethylsiloxanes were identified. The nongelled shell contained 332 µg/g of -----modified cyclic dimethylsiloxanes. The ----- content of these materials contained a maximum of two D^{Ph} units.

Shells from finished devices (exposed to gel filler) contained no detectable amounts of D₄ and at most a total of 34 µg/g of D₅-D₁₀. They contained a total of approximately 220 µg/g of linear dimethylsiloxanes, MDM-MD₁₇M. The total amount of vinyl-modified cyclic siloxanes were determined to be <52 µg/g and the total amount of -----modified cyclic siloxanes were <68 µg/g.

Sample Traceability (Cat. No./Lot No./Size)	NA/251121/ 100cc	354-1007/251121/100cc		
Compound	Nongelled Shell	Gel Filler (A)*	Shell (B)*	Whole Device (C)*
	(ug/g)			
D ₈ ²	<7.8	8.5	<7.6	<8.4
D ₉ ¹	<7.8	8.4	<7.6	<8.3
D ₁₀ ²	<7.8	11.5	<7.6	<10.92
D ₁₁ ²	<12.2	23.3	<12.9	<21.86
D ₁₂ ¹	22.2	35.3	17.6	32.92
D ₁₃ ²	48.5	51.0	27.8	47.85
D ₁₄ ²	148.3	118.7	77.6	113.11
D ₁₅ ¹	201.3	181.5	114.7	172.4
D ₁₆ ²	207.0	217.8	114.6	203.8
D ₁₇ ²	530.3	616.4	383.7	584.9
D ₁₈ ¹	387.8	560.7	356.0	533.0
D ₁₉ ²	272.88	450.9	292.2	429.4
D ₂₀ ²	521.62	657.8	303.9	609.9
D ₂₁ ¹	325.69	845.6	328.0	775.5
Linear Dimethyl Siloxanes				
MD ₇ M ¹	ND	<1.5	ND	<1.3
MD ₈ M ¹	ND	1.7	ND	1.5
MD ₉ M ¹	ND	3.2	ND	2.8
MD ₁₀ M ¹	ND	7.2	NA	6.2
MD ₁₁ M ²	ND	13.5	<11.2	<13.2
MD ₁₂ M ¹	ND	37.2	20.1	34.8
MD ₁₃ M ²	ND	54.6	29.3	51.2
MD ₁₄ M ²	ND	66.1	40.2	62.6
MD ₁₅ M ²	ND	70.0	41.5	66.2
MD ₁₆ M ³	ND	57.2	40.0	54.9
MD ₁₇ M ²	ND	64.9	38.1	61.3
Vinyl-Modified Cyclic Dimethylsiloxanes				
D ^{vi} D ₁₄ ^{2,4}	ND	6.8	ND	5.9
D ^{vi} D ₁₅ ^{2,4}	ND	10.1	NA	8.8
D ^{vi} D ₁₆ ^{2,4}	ND	14.0	<16.7	<14.4
D ^{vi} D ₁₇ ^{2,4}	ND	26.1	ND	22.6
D ^{vi} D ₁₈ ^{2,4}	ND	40.6	NA	35.1
D ^{vi} D ₁₉ ^{2,4}	ND	25.0	<35.1	<26.4

Sample Traceability (Cat. No./Lot No./Size)	NA/251121/ 100cc	354-1007/251121/100cc		
Compound	Nongelled Shell	Gel Filler (A)*	Shell (B)*	Whole Device (C)*
	(ug/g)			
----- Modified Cyclic Dimethylsiloxanes				
---	<8.9	ND	ND	ND
---	<8.9	ND	ND	ND
---	<8.9	ND	ND	ND
-- --	48.4	ND	14.4	2.0
-- --	37.1	ND	<9.9	<1.3
-- --	58.9	21.9	<9.9	<20.2
-- --	78.6	19.8	13.6	19.0
-- --	21.4	ND	<9.9	<1.3
-- --	23.1	ND	<9.9	<1.3
-- --	<8.9	ND	ND	ND
-- --	<8.9	ND	ND	ND
-- --	<8.9	ND	ND	ND
Miscellaneous Siloxanes				
Siloxane ³	ND	4.2	1.8	3.9
Residues of Solvents and Plasticizers				
o-Xylene ²	ND	<0.4	ND	<0.4
Di(Ethylhexyl) Phthalate ¹	<11.2	ND	ND	ND
Total Semivolatiles (ug/g)	<3055.8	<4350.1	<2403.8	<4086.7

ND = Not Detected, S/N <3.0

NA = Not Applicable. At least one of the replicates has a ND value.

Data preceded with a "<" symbol meaning a less than method detection limit value was measured in the sample or individual component

* - C = whole device calculation = $(A \cdot 98.1102 + B \cdot 15.3504) / (98.1102 + 15.3504)$

¹ Measurement based on external and internal standard calibrations.

² Due to unavailability of external standards, measurement is estimated, based on calibrated response factors of closest homologue.

³ Measurement based on the response factor of closest internal standard.

⁴ Tentative identification based on MS pattern.

5.2.3 Nonvolatiles Analysis

5.2.3.1 Gel

Gel extractables analysis yielded one polydimethylsiloxane compound with M_w of 53,900 and corresponding polydispersity (M_w/M_n) of ~2.4.

UV/Vis detection did not reveal the presence of any phenyl substituted materials. See Table 5-5 for a tabulation of results.⁷

5.2.3.2 Shell

Extracts of shell assemblies from gel-filled devices did not contain any high molecular weight ----- substituted polymer. For device shells processed with gel, some ----- substituted polysiloxane compounds were observed by UV/Vis detection with weight average molecular weight (M_w) of ~170-770. RI detection for methyl substituted polysiloxanes indicated a single peak M_w ~17,400 and polydispersity of ~1.8 in extracts from the shell assembly of a filled device. See Table 5-6.

Extractables of device shells processed without gel yielded a more concentrated representation of the shell components by UV/Vis detection. Phenyl polymer, oligomer and monomeric species were detected with weight average molecular weight (M_w) ~ 170-61,600. Quantitation of ----- substituted polysiloxanes, as determined by UV/Vis detection, indicated the presence of several compounds with concentration of ~ <32-620 $\mu\text{g/g}$ (<4-70 $\mu\text{g/g}$ on a whole device weight basis). The extract of shells processed without gel yielded two dimethylsiloxane species with molecular weight averages of ~341,100 and ~4,820. The high molecular weight species represented less than 10% of the total peak area. See Tables 5-7 and 5-8.

5.2.3.3 Conclusion

The gel and shell samples from finished devices contained polydimethylsiloxane polymers ranging from 17,400 to 54,000 weight average molecular weight. The polymer from the gel was more polydisperse than polymer extracted from shells. The gel samples contained no ----- substituted polymers above the quantification limit of the method. Four phenyl substituted species were identified in the shell samples from finished devices. These are very low molecular weight compounds in a range that were identified and quantified more accurately in the semivolatiles analysis (see Section 5.2.2).

Polydimethylsiloxane polymers with a weight average molecular weight range of approximately 4,800 to 341,000 were identified in nongelled shell sample extracts. ----- polymers ranging in weight average molecular weight from 3900 to 62,000 were found in the nongelled shell samples. Low concentrations of many of the same ----- compounds found in the nongelled shells samples were also present in the shell samples exposed to gel. These materials were more accurately identified and quantified through the semivolatiles analytical procedure.

⁷ C. S. Puckett, Report Number CP 359, *Idem*.

The high molecular weight polymers found in the shell and gel samples are typical of the processing of the silicone intermediate for gel-filled mammary implants.

Table 5-5. Nonvolatile Extractables Analysis of Gel Filler from Siltex Round Moderate Profile Gel Mammary Implants

Gel from Gel-Filled Mammary Implant (100 cc), Lot Number 251121, SiTech Raw Materials, SiTech Raw Materials			
Tentative Compound Identity	M_w	M_n	Polydispersity
Polysiloxane ^a	53,900	22,300	2.4

^aPolydimethylsiloxane Calibration; (Agilent ChemStation Rev. A.09.01 [1206], 1100 RI Detector)

Table 5-6. Nonvolatile Extractables Analysis of Shell Samples from Siltex Round Moderate Profile Gel Mammary Implants

Finished Device Shell Assemblies of Siltex Round Moderate Profile Gel Mammary Implants (100cc), Lot Number 251121, SiTech Raw Materials			
Tentative Compound Identity	M_w	M_n	Polydispersity
Polydimethylsiloxane ^a	17,400	9900	1.8
----- Polysiloxane ^b	770	770	1.0
-----	550	540	1.0
-----	260	250	1.0
-----	170	170	1.0

^aPolydimethylsiloxane Calibration, (Agilent ChemStation Rev. A.09.01 [1206], 1100 RI Detector connected in series)

^bUltraviolet/Visible Spectrophotometric Detection with Polystyrene Calibration (Agilent ChemStation Rev. A.09.01 [1206])

Table 5-7. Nonvolatile Extractables Analysis of Nongelled Shells from Siltex Round Moderate Profile Gel Mammary Implants

Nongelled Shells from Siltex Round Moderate Profile Prostheses, (100 cc), Lot # 251121, SiTech Raw Materials			
Tentative Compound Identity	M _w	M _n	Polydispersity
Polydimethylsiloxane ^a	341,100	270,100	1.3
Polydimethylsiloxane ^a	4,820	3,860	1.2
----- HTV Polymer ^b	61,600	49,100	1.3
----- Oligomer ^b	3,900	2,320	1.7
----- ^b	790	780	1.0

-----	560	550	1.0
-----	290	280	1.0
-----	170	170	1.0

^aHewlett Packard Refractive Index 1100 with Polydimethylsiloxane Calibration

^bUltraviolet/Visible Spectrophotometric Detection (Agilent ChemStation Rev. A.09.01 [1206])

Table 5-8. Nonvolatile Extractable Compound Concentrations of Non-gelled Shell From Siltex Round Moderate Profile Shells

Nongelled Shell from Siltex Round Moderate Profile Prostheses (100cc), Lot #251121, SiTech Raw Materials		
Tentative Compound Identity ^a	Shell Concentration (µg/g)	Device Concentration (µg/g)
----- HTV Polymer	72	8
-----er	623	70
-----	323	36
-----	621	70
-----	38	4
-----	< 32	< 4

^aUltraviolet/Visible Spectrophotometric Detection (Agilent ChemStation Rev. A.09.01 [1206])

5.3 Sol Fraction, Equilibrium Swell Ration and Crosslink Density⁸

Three (3) Siltex™ Round Moderate Profile Gel-Filled devices (100 cc) were used to obtain the test samples used in this study. Test devices were taken from finished product inventory. The texture layer, patch and patch components were produced from SiTech raw materials. The only non-SiTech material was the small amount, approximately two drops, of dip coat used to seal the needle hole in the patch after the gel precursor is injected into the shell. The dip coat is sourced from Dow Corning.

⁸ C. S. Puckett, Report Number CP 361, *Sol Fraction, Equilibrium Swell Ratio, and Crosslink Density of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, February 6, 2003.

Gravimetric data⁹ was used to calculate sol fraction and equilibrium swell ratio of the shell and gel post extraction of the soluble fraction. Swelling ratio of swollen and dry volumes was used to characterize the crosslinked polymer networks.

The shell and gel are completely cured during normal processing conditions to produce finished product. If not, equilibrium swell ratio and sol fraction would not be representative. Gel and shell samples were subjected to exhaustive extraction conditions (M/V 1/200) before and after an additional thermal cure step consisting of 240 minutes at ~164°C. Three device replicates for each finished product sample of shell and gel were tested. Equilibrium swell ratio and percent extractable and subsequently calculated molecular weight between crosslinks (M_c) and crosslink density (ρ_c) for the shell and gel were not significantly changed ($p \geq 0.05$) after the additional thermal post cure treatment. This demonstrates that the gel and shell exhibited complete cure after manufacture.

5.3.1 Gel

Gravimetric data on the gel samples resulted in calculated values for polymer molecular weight between crosslinks (M_c) of $\sim 6.9 \times 10^5$ g/mol, crosslink density (ρ_c) of 1.5×10^{-6} mol/cc, toluene equilibrium swell ratio of ~ 37 and total extractables of $\sim 74\%$. See Table 5-9.

5.3.2 Shell

Shell samples were extracted with toluene solvent as described above. For shell samples a mass-of-sample/solvent volume (M/V) ratio of 1/100 was used. One extraction step was sufficient for exhaustiveness for shell samples. Equilibrium swell ratio was determined for toluene to be 3.7 and total extractables of ~ 8.3 weight %. Calculation of polymer crosslink density, etc, required that a correction for the amorphous silica reinforcing filler be applied. It was assumed that the silica filler is approximately 22 weight % of the shell elastomer. Densities of the shell and solvent are 1.1 g/cc, 0.98 g/cc and 0.87 g/cc, respectively.

The following results were calculated from the gravimetric determinations on the samples: Network Chain Molecular Weight (polymer molecular weight between crosslinks, M_c) $\sim 8.4 \times 10^3$ g/mol, Molar Crosslink Density (ρ_c) $\sim 1.3 \times 10^{-4}$ mol/cc and Crosslink Chain Density ($\rho_c N_{AV}$) $\sim 7.90 \times 10^{19}$ chain/cm³. See Table 5-9.

⁹ C. S. Puckett, Report Number CP 361, *Sol Fraction, Equilibrium Swell Ratio, and Crosslink Density of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, February 6, 2003.

Table 5-9. Crosslink Density, Swell and Extractables of Gel and Shell Samples from Siltex™ Round Moderate Profile Gel Mammary Implants

Sample Type	M_c (g/mol)	ρ_c (mol/cm ³)	$\rho_c N_{AV}$ (chain/cm ³)	Swell Ratio	Extractables (%)	Recovery (%)
Finished Device Gel, Sample 361213-1 to 361215-1, M:V ~ 1:100						
X	6.89E+05	1.46E-06	8.81E+17	36.9	73.8	100.1
S	1.38E+05	0.30E-06	1.83E+17	4.0	3.5	0.1
CV	0.20	0.21	0.21	0.11	0.05	< 0.01
Finished Device Shell, Sample 361101-1 to 361103-1, M:V ~ 1:200						
X	8.40E+03	1.31E-04	7.90E+19	3.7	8.3	98.0
S	0.34E+03	0.05E-04	0.32E+19	0.1	0.2	0.4
CV	0.04	0.04	0.04	0.01	0.02	< 0.01

M_c = Network Chain Molecular Weight (g/mol)

ρ_c = Molar Crosslink Density (mol/cm³)

$\rho_c N_{AV}$ = Crosslink Chain Density (chain/cm³)

X = Average

S = Standard Deviation

CV = s/X

5.3.3 Conclusion

Equilibrium swell ratio and sol fraction were measured and used to calculate molecular weight between crosslinks, crosslink density, and percent extractable. The data support the fact that the gel has a very lightly crosslinked molecular architecture when compared to the shell elastomer. In addition, the data obtained before and after an additional post cure showed no statistical change, thus demonstrating that the shell and gel exhibited complete cure after manufacturing.

5.4 Heavy Metals

Heavy metal target analytes were chosen according to the metals group known to pose health hazards at various threshold levels, which includes Ag, As, Ba, Be, Cd, Co, Cr, Cu, Hg, Mg, Mo, Ni, Pb, Pt, Sb, Se, Sn, Ti, V and Zn. This is the Title 26 metals group with the addition of magnesium, platinum, and tin.¹⁰

Eight Siltex Round Moderate Profile Gel-Filled Prostheses were selected for testing as being representative of the gel-filled devices in this submission. These devices were fabricated with SiTech elastomers for texturing, shell, gel, and patch assembly components, and Dow Corning/ dip coat fill. The samples were desiccated under vacuum at room temperature for 24 hours, and weights were recorded.

Samples of gel and shells were aqueously extracted using Type I buffered leaching fluid for inorganic heavy metals according to EPA Method 1311 "Toxicity Characteristic

¹⁰ Julian, N. Report CP 360, *Extractable Metals Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, February 17, 2003.

Leaching Procedure"¹¹ (TCLP). Three serial extractions were performed at a mass to volume ratio (M/V) of 1/20 by immersion in the aqueous leaching fluid for 120 hours at 37°C.

Extraction of organometallic compounds was performed with Soxhlet apparatus using methylene chloride. For each sample, three serial extractions were done and the extracts were combined. Shell samples were extracted 20 hours each time by this technique using M/V of approximately 1/20. For gel samples a period of 30 hours was used for each extraction repetition, with sample size of approximately 6 g and 900 mL solvent.

The samples were analyzed by inductively coupled plasma/mass spectroscopy (ICP/MS) for all target analytes. Quality control procedures and qualifications included the use of standards, method blanks, and duplicate spiked samples for the gel and for the shell.¹⁰ Three standard concentrations were used for each element. Each calibration curve was evaluated for linearity and verified by a standard not used for calibration. Exhaustive extraction was demonstrated by comparison of sample results from serial extractions based upon aqueous and organic solvents. Spiked samples were used to determine recovery through the complete sample preparation process, as well as after the organic digestion stage of the procedure.

For heavy metals with any results above their respective method detection limits, the results are in Table 5-10. Results are presented by extraction samples of the shell and gel components separately, and then the results on each extraction sample for each component were added together and the result for the complete device was calculated by normalization.

Table 5-10. Heavy Metals Analysis of Devices Made With SiTech Gel and Shell (µg/g)

Element*	Shell Extractables		Gel Extractables		Complete Device**
	Aqueous	Organic	Aqueous	Organic	
Mg	0.454	0.016	0.373	ND	0.385
Ti	ND	0.004	ND	0.029	0.026
Cr	ND	ND	ND	0.017	0.015
Co	ND	ND	0.059	ND	0.051
Ni	0.017	0.010	0.048	0.0049	0.050
Cu	0.024	ND	0.0067	0.018	0.025
Zn	0.126	0.011	ND	ND	0.017
Cd	0.0024	0.0010	0.0019	ND	0.0021
Sb	0.020	0.0016	0.0025	0.010	0.014
Ba	0.0020	ND	ND	ND	0.0003
Pt	0.055	0.078	0.018	0.305	0.30
Hg	0.003	ND	ND	ND	0.0004
Pb	0.015	0.0031	0.0085	0.0019	0.011

* - elements targeted but not specifically listed were "ND" in all extracts.

** - Complete device = [(total shell conc. * 14.5) + (total gel conc. * 99.4)]/(14.5 + 99.4)

¹¹ USEPA Method 1311, "Toxicity Characteristic Leaching Procedure." US Environmental Protection Agency, Office of Solid Waste and Emergency Response. SW 846. Washington, DC. 1986 and updates.

The valence state of the platinum catalyst used in the high temperature vulcanization reaction of vinyl hydrosilation is zero. (A further discussion of the valence state is provided in Section 5.4.1 Platinum of this chemistry module.) Of the total platinum material added to catalyze the silicone polymerization, only 0.30 µg/g of that amount is extractable under both the aqueous and organic exhaustive extraction techniques used here. Tin, used to catalyze the dip coat fill, was not detected. This is expected due to the small amount of dip coat fill used.

Where a heavy metals result was below the detection limit, ND was reported in Table 5-10 (above). The worst case assumption would be that samples could contain the amount of heavy metal detected PLUS an amount equal to the detection limit where ND was reported in the table above. Table 5-11 (Worst Case Heavy Metals Content in SiTech Gel, SiTech Shells, and Complete Devices) presents these worst case calculated amounts.

Table 5-11. Worst Case Heavy Metals Content in SiTech Gel, SiTech Shells, and Complete Devices (µg/g)

Element	Shell Extractables		Gel Extractables		Complete Device*
	Aqueous	Organic	Aqueous	Organic	
Be	0.0031	0.0032	0.0031	0.0032	0.006
Mg	0.454	0.016	0.373	0.0060	0.391
Ti	0.0068	0.004	0.0068	0.029	0.033
V	0.16	0.14	0.16	0.14	0.310
Cr	0.012	0.012	0.012	0.017	0.028
Co	0.00038	0.00048	0.059	0.00048	0.052
Ni	0.017	0.010	0.048	0.0049	0.050
Cu	0.024	0.00046	0.0067	0.018	0.025
Zn	0.126	0.011	0.015	0.0040	0.034
As	0.070	0.053	0.070	0.053	0.123
Se	0.046	0.023	0.046	0.023	0.069
Mo	0.00060	0.00033	0.00060	0.00033	0.001
Ag	0.00072	0.00028	0.00072	0.00028	0.001
Cd	0.0024	0.0010	0.0019	0.00050	0.0025
Sn	0.0029	0.0014	0.0029	0.0014	0.004
Sb	0.020	0.0016	0.0025	0.010	0.014
Ba	0.0020	0.00035	0.00028	0.00035	0.001
Pt	0.055	0.078	0.018	0.305	0.299
Hg	0.003	0.0028	0.00091	0.0028	0.004
Pb	0.015	0.0031	0.0085	0.0019	0.011

* - Complete device = [(total shell conc. * 14.5) + (total gel conc. * 99.4)]/(14.5 + 99.4)

5.4.1 Platinum

Platinum is used as a catalyst for hydrosilylation or condensation cure reactions of polysiloxanes. Gel mammary implants rely upon this polymer crosslinking to produce the elastomeric shell and the gel filler. This section will address Mentor's information on the subject of platinum in gel-filled mammary prostheses and the valence state of the platinum metal.

5.4.1.1 Platinum Determination

The platinum catalyst is prepared from chloroplatinic acid (H_2PtCl_6) and divinyltetramethyldisiloxane $[(\text{CH}=\text{CH}_2)(\text{CH}_3)\text{SiOSi}(\text{CH}_3)_2(\text{CH}=\text{CH}_2)]$. During processing, it is neutralized with sodium bicarbonate in the presence of isopropyl alcohol yielding a silicone complex $[\text{Pt}_2((\text{CH}=\text{CH}_2)(\text{CH}_3)_2\text{SiOSi}(\text{CH}_3)_2(\text{CH}=\text{CH}_2))_3]$.¹⁻⁴ This platinum complex catalyst is used in both shell dispersion and gel raw materials.

Platinum inorganic and organometallic compounds can be synthesized with several common oxidation states; Pt(0), Pt(II) and Pt(IV).⁵ Less common oxidation states include Pt(I), Pt(V) and Pt(VI) as metal clusters and fluoro compounds respectively. The oxidation state of platinum in the silicone complex catalyst is Pt(0) as discussed below.

Platinum quantitation in gel mammary implants is conducted as part of extractable heavy metals testing. The sample preparation and subsequent analysis is designed to segregate and target inorganic and organometallic platinum compounds. This is achieved with an aqueous followed by an organic extraction of mammary shell and gel components separately. The aqueous extraction is performed using Toxicity Characteristic Leaching Procedure.⁶ The organic extraction utilizes a methylene chloride Soxhlet technique. Inductively coupled plasma spectroscopy with atomic emission and mass spectrometric detection (ICP/AES and ICP/MS) provide the extract instrumental analysis. Gel mammary implants have been tested using this methodology and include demonstration of exhaustiveness of the extraction and validation.^{7, 8} Results indicate that the concentration of platinum as inorganic compounds is 0.023 $\mu\text{g/g}$ (per unit weight 100 cc device). Platinum as organometallic compounds is 0.276 $\mu\text{g/g}$ (per unit weight 100 cc device). It is assumed, based upon the rationale presented below, that organometallic platinum is present in the Pt(0) valence state.

References:

- [1] "Master Access File: Silicone Gel," MAF No. 1039, SiTech, LLC, Irvine, TX.
- [2] "Master Access File: Dimethyl Silicone Dispersion," MAF No. 1040, SiTech, LLC, Irvine, TX.

- [3] "Master Access File: ----- Silicone Dispersion," MAF No. 1041, SiTech, LLC, Irvine, TX.
- [4] "Master Access File: ----- Silicone Elastomer," MAF No. 1115, SiTech, LLC, Irvine, TX.
- [5] Cotton, F. A., Wilkinson, G., "Advanced Inorganic Chemistry," John Wiley & Sons, New York, 1980.
- [6] "Toxicity Characteristic Leaching Procedure," USEPA Method 1311, Revision 0,1-35, July, 1992.
- [7] Boggess, K., "Heavy Metals Analysis of Gel-Filled Mammary Prostheses," Mentor Corporation, Report CP 279, Midwest Research Institute, Project No. 305546, Santa, Barbara, CA, December 1, 1999.
- [8] Julien, N., "Extractable Heavy Metals Analysis of Round Profile Gel Mammary Implants: Qualification of Manufacturing Process Modifications," Mentor Corporation, Report CP 360, Midwest Research Institute, Project No. 310420, Santa Barbara, CA, February 14, 2003.

5.4.1.2 The Chemical Nature of Residual Platinum in Silicone Breast Implants from Published Literature

*Prepared by: Robert A. Scott, Ph.D.
Professor and Department Head
University of Georgia
Department of Chemistry
412 Chemistry Building
Athens, GA 30602-2556*

[See the Appendices for Prof. Scott's curriculum vitae.]

The silicone polymers (elastomer, gel, etc.) used in the manufacture of breast implants are produced by a catalytic process that polymerizes vinyl-containing siloxane monomers. The chemical process that couples the monomers is the addition of Si-H bonds across the vinylic C=C double bonds, a reaction known as hydrosilylation (or hydrosilation)¹. The most active catalysts for hydrosilylation contain platinum (Pt) and these are used in most commercial production. Even though these Pt catalysts are very efficient (functional at significant rates down to 10^{-6} - 10^{-7} mole ratio Pt:monomer¹), a small amount of residual Pt remains in the polymerized product. Since some of the valence states of Pt are of considerable toxicological concern, it is worth examining the available evidence concerning the chemical state of this Pt.

As for all transition metals (including the noble metals, of which Pt is an example), organometallic compounds exist for different oxidation (valence) states of Pt. Elemental Pt (denoted Pt(0)) is uncharged and less reactive (thus the term "noble" metal), whereas removal of two or four electrons (oxidation) to Pt(II) or Pt(IV), respectively, generates more

reactive metal ions, for which many compounds are known. (For example, the widely used cisplatin antitumor compounds that bind to DNA bases contain Pt(II).) These higher oxidation states are of significantly more toxicological concern than is Pt(0). It is common to purchase higher oxidation state Pt compounds as the chloride adducts, hexachloroplatinate(IV) dianion ($4+$ for Pt(IV) plus $6(-1)$ for chlorides = -2) and tetrachloroplatinate(II) dianion ($2+$ for Pt(II) plus $4(-1)$ for chlorides = -2). The question addressed herein is the valence of the residual Pt that remains after hydrosilylation catalysis of silicone polymerization.

Virtually all the commercial catalyst preparations used for hydrosilylation are based on either Karstedt's "precatalyst"² or on Speier's catalyst³. Karstedt's catalyst has been structurally characterized and is known to consist of Pt(0) linked to three vinyl substituents of the disiloxane components⁴. The neutral olefinic ligands tend to stabilize Pt(0) because of electroneutrality. Speier's catalyst is prepared from hexachloroplatinic(IV) acid and 2-propanol, but exhibits a long induction period in catalysis of hydrosilylation, suggesting a required transformation of the Pt species to form the active catalyst⁵.

Regardless of the Pt valence in the starting catalyst, the important concern is the Pt valence of the residual (spent) catalyst after polymerization. Although there are numerous studies of Pt-catalyzed hydrosilylation available¹, most concentrate on the mechanism and organic products. The best work available to characterize the chemical nature of the Pt before, during, and after catalysis is that by Stein, Lewis, and coworkers⁵⁻⁷. They employed several techniques, including the solution X-ray techniques of X-ray absorption spectroscopy (XAS) and small-angle X-ray scattering (SAXS) to investigate the Pt coordination environment before, during, and after catalysis in the 2-50 Å size region.

In particular, their work showed that the original hypothesis of colloidal Pt as the active catalyst⁸ was not supported by these techniques and a new mechanism in which homogeneous catalysis occurred at mononuclear Pt species fit all their observations⁵. This mechanism, now accepted by most researchers in the field, involves an initial Pt(0) catalyst precursor containing olefinic ligands (the vinyl substituents of siloxane monomers, such as are present in Karstedt's precatalyst). This Pt(0) precursor reacts with a Si-H bond on another monomer in a reaction generally known as "oxidative addition" to form a transient formally Pt(II) intermediate with additional Pt-Si and Pt-H bonds⁵. Migratory insertion of an olefinic ligand into the Pt-H bond provides the Pt-alkyl ligand which reductively eliminates forming the Si-alkyl product (the growing polymer in polymerization) and a Pt(0) species that then picks up another olefinic ligand from solution. Thus, although Pt(II) species are transiently produced in the mechanism, the dissociation of the polymer product

occurs by "reductive elimination" (the reverse of oxidative addition) that reduces the Pt(II) intermediate back to Pt(0). The Pt(II) intermediates are unstable to this reductive elimination and thus, both the active catalyst and the spent catalyst (after polymerization) are expected to be Pt(0) oxidation state.

The critical importance of the use of X-ray absorption spectroscopy in these studies is that, in addition to providing local structural information about the Pt coordination sphere, this technique can also provide a direct measure of Pt oxidation state by use of the X-ray absorption edge⁶. These workers were able to show convincingly that the oxidation state of the Pt remaining after hydrosilylation catalysis was *identical* to that of the Pt catalyst precursor, which in this case was Karstedt's precatalyst, containing Pt(0)⁵. More importantly, the oxidation state of the residual Pt was *independent* of the starting catalyst. Even when Speier's (Pt(IV)) catalyst was used, the final Pt oxidation state was still Pt(0)⁵. Not only does this show that only elemental Pt is the product of these catalyses, but it also suggests that all Pt-based catalysts operate through an identical mechanism for hydrosilylation.

In summary, theory predicts and all experimental evidence supports the domination of the Pt(0) oxidation state in both the active catalyst and the residual Pt remaining in these silicone polymers after catalysis. No evidence exists for the presence of higher oxidation state species in these products.

References:

- [1] Harrod, JF, "Hydrosilation Catalysis," In *Encyclopedia of Inorganic Chemistry* King, RB, Ed., Wiley: Chichester, 1995, Vol. 3, pp. 1486-1496.
- [2] Karstedt, BD, U.S. Patent 3,775,452, 1973.
- [3] Speier, JL, Webster, JA, Barnes, GH, "The Addition of Silicon Hydrides to Olefinic Double Bonds. Part II. The Use of Group VIII Metal Catalysts," *J. Am. Chem. Soc.* 1957, 79, 974-979.
- [4] Hitchcock, PB, Lappert, MF, Warhurst, NJW, "Synthesis And Structure of a Rac-Tris (Divinyldisiloxane)Diplatinum(0) Complex and Its Reaction With Maleic-Anhydride," *Angew. Chem., Intl. Ed. Engl.*, 1991, 30, 438-440.
- [5] Stein, J, Lewis, LN, Gao, Y, Scott, RA, "In Situ Determination of the Active Catalyst in Hydrosilylation Reactions Using Highly Reactive Pt(0) Catalyst Precursors," *J. Am. Chem. Soc.*, 1999, 121, 3693-3703.
- [6] Lewis, LN, Colborn, RE, Grade, H, Bryant, GL, Jr., Sumpter, CA, Scott, RA, "Mechanism of Formation of Platinum(0) Complexes Containing Silicon-Vinyl Ligands," *Organomet.*, 1995, 14, 2202-2213.
- [7] Lewis, LN, Stein, J, Smith, KA, Messmer, RP, LeGrand, DG, Scott, RA, In *Progress in Organosilicon Chemistry* Marciniak, B., Chojnowski, J., Eds., Gordon and Breach: Amsterdam, 1995, pp. 263.

[8] Harrod, JF, Chalk, AG, In *Organic Synthesis via Metal Carbonyls*
Wender, I, Pino, P, Eds., Wiley: New York, 1977, pp. 673-703.

5.5 Infrared Spectral Analysis

Infrared spectral analysis was performed on samples of gel and shells from finished PMA devices made with all five manufacturing changes^{12,13} as stated earlier in this section of the Module. The infrared spectra were obtained using a Fourier transform infrared spectrophotometer (FT-IR) with an attenuated total reflectance accessory (ATR).

This technique is qualitative, and shows absorbance bands that are representative of the composition of silicone materials used in the finished devices. Specifically, the spectra are typical of polydimethylsiloxane, which is the prevalent moiety in each of the compositions. There was no evidence of ----- character, which would show in the range of 3020 to 3080 cm^{-1} if present in sufficient amount to be detected. That would typically require the presence of a few percent of the ----- moiety in the composition.

Characteristic absorbance bands are listed in Table 5-12. IR spectra of shell, gel, laser marked versus unmarked shell areas, dipcoat reinforcement, and the patch can be found in Figures 5-1 to 5-6.

Table 5-12. Characteristic Absorbances of Poly Dimethyl Siloxane Materials

Approximate Wavenumber (cm^{-1})	Chemical Functionality Assignment
2961 or 2964	Symmetrical C-H stretching in CH_3 group
2905 or 2906	Asymmetrical C-H stretching in CH_3 group
1442	C-H deformation in CH_3 group
1412	Asymmetrical CH_3 deformation in Si-CH_3 group
1258 or 1461	Symmetrical CH_3 deformation in Si-CH_3 group
1000-1100	Asymmetrical Si-O-Si stretching
863 or 864	Si-C stretching
787 or 799	Si-C stretching

By FT-IR absorbance wavelength analysis and comparison to a library standard, the shell, gel, and various other samples tested from finished devices are made from polydimethylsiloxane of high purity. The spectra overlays of the laser marked area versus the unmarked area showed that there was no presence of additional functionality groups.

¹² Grace Chiang, Report CP 280, *Surface Chemical Composition of Dow, ASC, and SiTech Gel-Filled Mammary Prostheses*, November 21, 1999, Appendix D, IR Spectra of Samples.

¹³ Wenkai Ma, Report CP 362, *Infrared Spectral Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, February 10, 2003, Appendix C, IR Spectra of Samples.

5.6 *Silicone Fluid Component of Gel Formation*

In a letter from Thomas P. Banigan, QA/Regulatory Compliance Consultant to SiTech LLC¹⁴, Mr. Banigan stated "The information ... concerning the polymers used in the manufacture of the SiTech gel products supplied to Mentor are located within Master Access File MAF-1039 which have been submitted to the United States Food and Drug Administration. MAF-1039 consists of two sections:

- I.] *Masterfile Manufacturing Portion for GEL-2167/GEL2168, GEL-2167-1/GEL-2168-1*
- II.] *GEL-2167/GEL-2168, Testing Compendium.*"

The letter goes on to state that the compositions of the polymers included in the gel are presented in the Testing Compendium, Section 1, Exhibit 1. The polymer concentration in the gel formulation is presented in GEL-2167/GEL-2168 Manufacturing Portion, page 125, paragraph (I.) "Formulation" for part (A) and page 133 paragraph (I.) "Formulation" for Part (B). Note: GEL-2167/GEL-2168 is supplied as a 3:1, Part (A):Part (B) gel product.

Molecular Weight and Molecular Number for the gel intermediates formulation are shown in *Testing Compendium*, Section 5, Exhibit 17, Page 10. Viscosity data are provided in GEL-2167/GEL-2168 *Manufacturing Portions* page 84, paragraph IX, line 3.0 and page 93, paragraph IX, line 3.0. The degree of polymerization for the polymers in the gel intermediates are provided in the *Testing Compendium*, Section 5, Exhibit 19.

5.7 *Physical Properties of the Gel*

The cohesiveness of the gel used in the products covered by this PMA is addressed during finished product testing. Within this PMA's Manufacturing Module, QCIC 000167 Finished Device Testing (see Volume 6, page 868 of the Manufacturing Module) contains the requirement for this testing. Cohesion testing (per ASTM F 703-96) on sterile finished devices has been performed as part of the Product Performance Qualification testing to verify that the device gel meets the cohesion specification.

In addition to cohesion testing, an in-process penetrometer test is performed on a lot-to-lot basis during manufacturing to check that the penetrometer specification for the gel (between 3.0mm to 10.0mm) has been met. See the Manufacturing Module for additional information on the penetrometer testing.

5.8 *Chemical Characterization of Laser-Marked Patches*

Laser marking of the patch (which includes company name and logo, device volume, and manufacturing lot number) has recently been added as a feature on finished devices. Process qualifications and device validation were completed in the production facility and demonstrated that consistent marking could be obtained with no impact on device physical properties. Chemical characterization was completed prior to the

¹⁴ Letter from Thomas P. Banigan, QA/Regulatory Compliance Consultant to SiTech LLD, to Jerry R. Barber, Mentor Corporation, dated April 18, 2003. This letter is included in the Appendices of this module.

implementation of the process into manufacturing. The results of this characterization demonstrate that the laser marking process creates no new chemical species and the amorphous silica filler in the patch elastomer remains in that state¹⁵.

Characterization tests included photomicroscopy, infrared spectroscopy, gas chromatography/mass spectroscopy, organic elemental analysis, x-ray diffractometry, x-ray photoelectron spectroscopy and Raman spectroscopy.

Prototype samples consisted of silicone elastomer discs with a diameter of ~5 cm made from ----- representing a device patch component. One set of prototype samples was engraved with the company name, manufacturing lot number and volume using four (4) laser passes. These samples were prepared from vulcanized sheeting without further processing. Silicone elastomer control discs were also prepared without laser printing. An additional set of prototype samples was engraved with a 1 cm spot using three (3) and nine (9) laser passes. Prototype finished product was also assembled with textured shells ----- without gel filler and engraved with the company name, logo, manufacturing lot number and volume using five (5) laser passes. These samples were processed according to standard manufacturing operating procedures with the exception that the laser marking font was larger than normal and the writing orientation on the patch was somewhat different than the current finished device. These differences would have no effect on the outcome of the chemical characterization. The larger font might, in fact, present a more stringent test since the laser will impinge the surface for a longer period of time in order to produce the larger font. In addition to sample testing, several reference standards were examined with various techniques: amorphous silica, crystalline silica, amorphous carbon and silicon carbide.

5.8.1 Optical Microscopy

This technique was used to measure the laser spot size on the surface of samples and to determine the depth of penetration into the matrix. Samples examined were the silicone elastomer disc surface with laser marking.

The surface micrographs reveal that the laser pulse spot has a diameter of ~50 μm and a depth of ~200 μm .

5.8.2 Infrared Spectroscopy

Fourier transform infrared spectroscopy (FTIR) was used to determine the chemical functional groups on the elastomer surface. Samples included silicone elastomer discs with laser engraved marking and spots and control.

The FTIR spectra of the silicone elastomer disc with laser marking are representative of siloxane and hydrocarbon bonds. No significant differences were observed between the sample subjected to laser marking and the control.

¹⁵ G. M. Allen, Report CP 353, *Chemical Testing of Laser Marked Patches for Mammary Implants*, November 27, 2002.

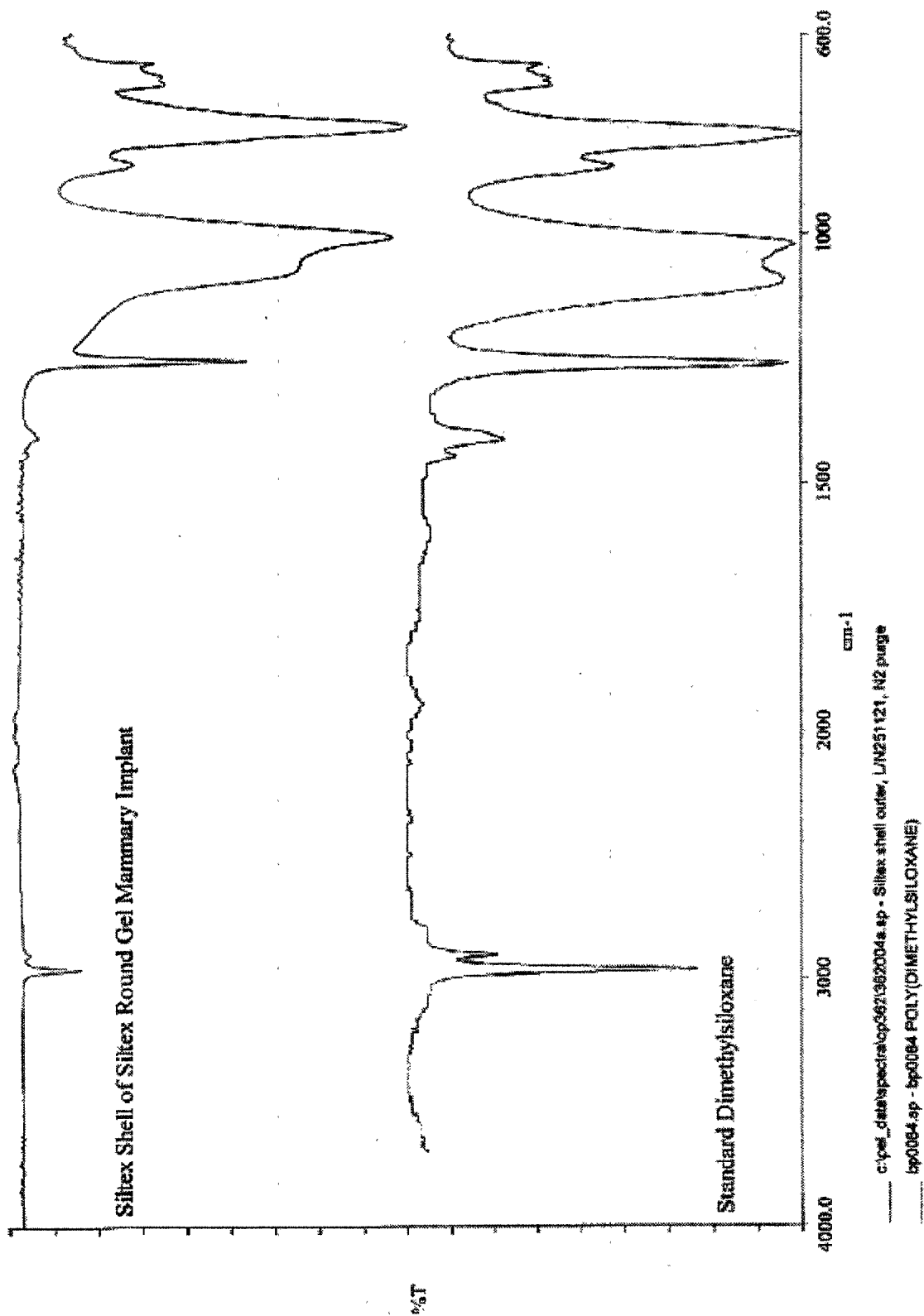


Figure 5-1. IR Spectra Overlay of Siltex Round Gel Mammary Implant and Dimethylsiloxane

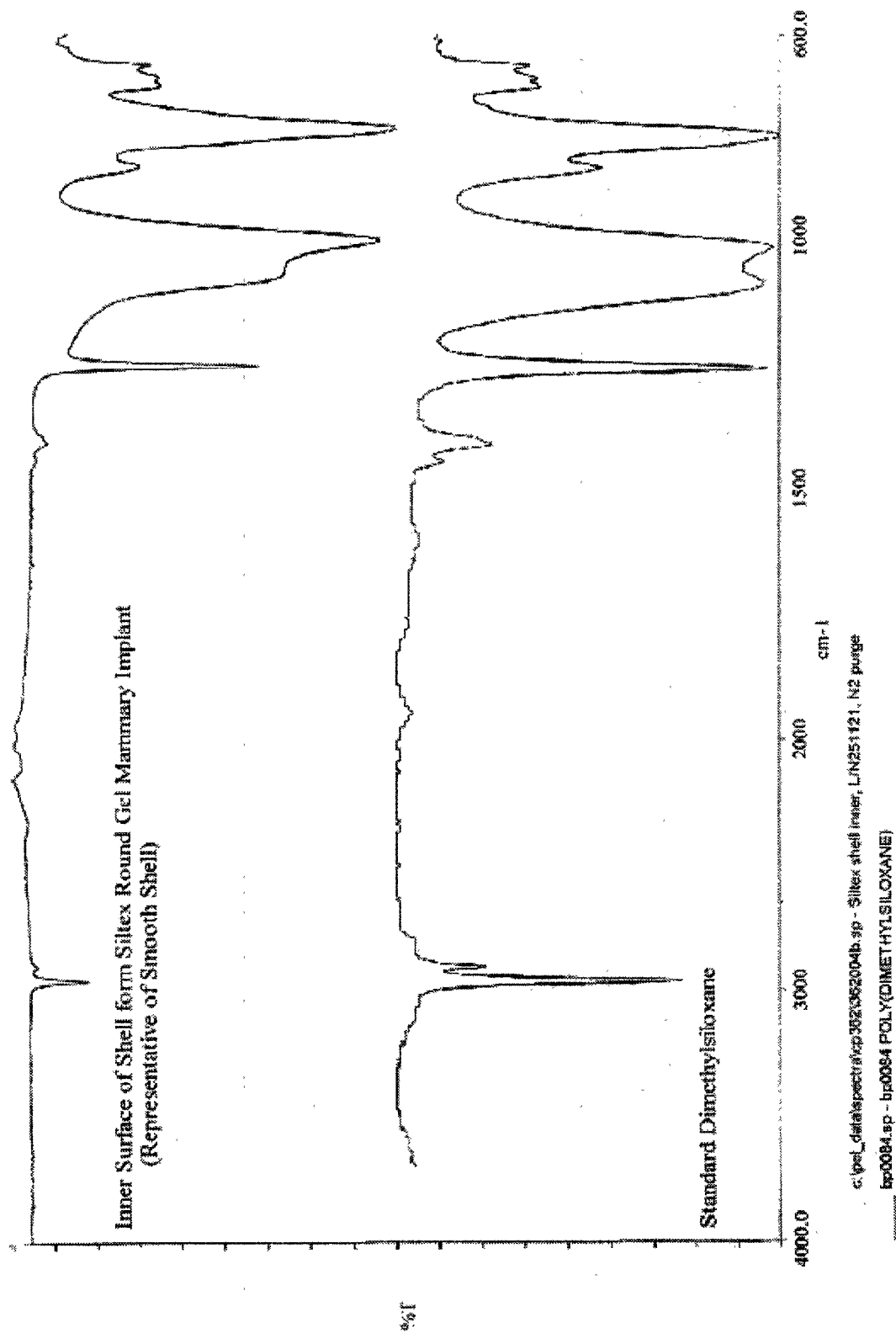


Figure 5-2. IR Spectra Overlay of Inter Surface Siltex Shell from Siltex Round Gel Mammary Implant and Dimethylsiloxane

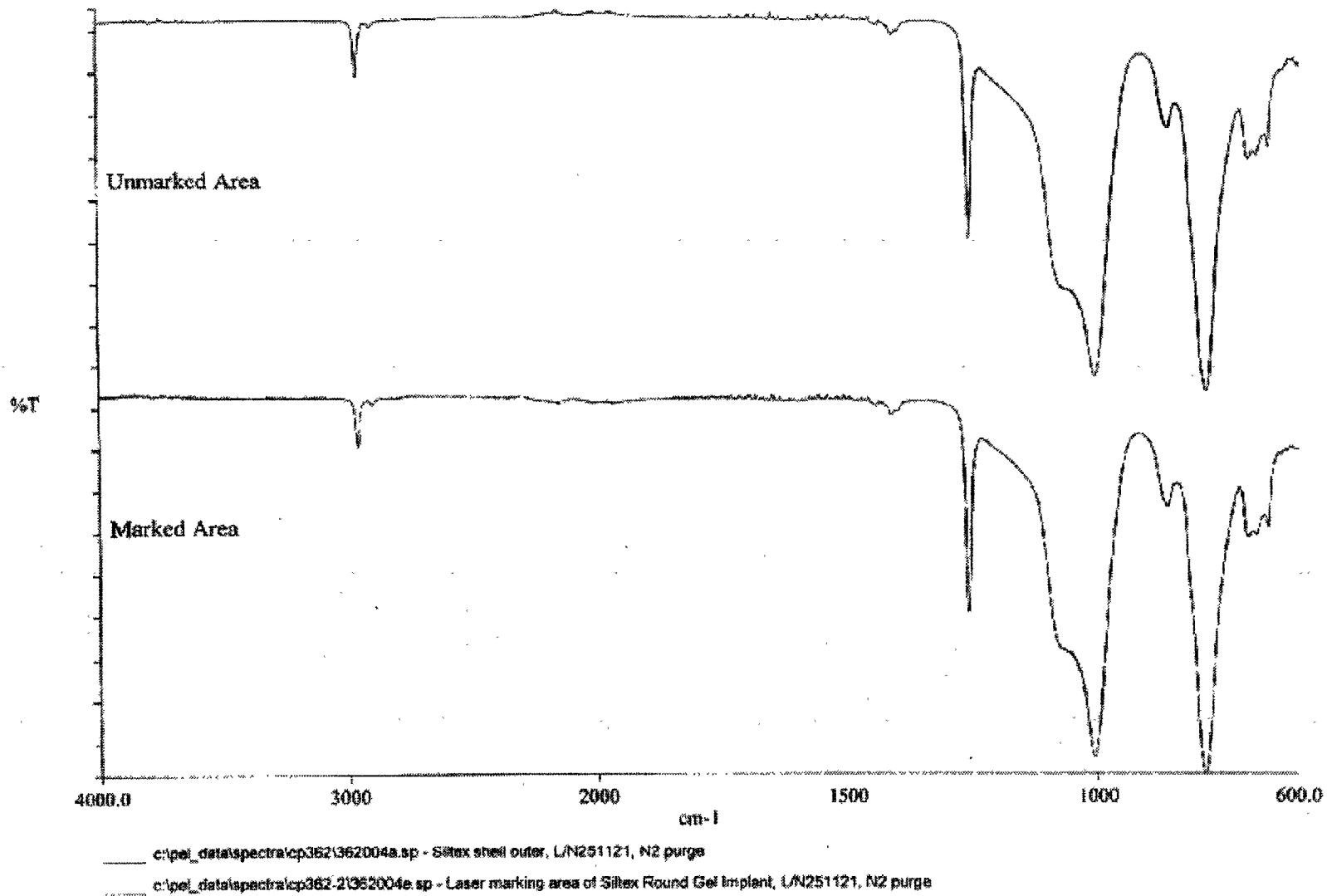


Figure 5-3. IR Spectral Comparison of Laser Marked and Unmarked Areas of Siltex Round Gel Mammary Implant

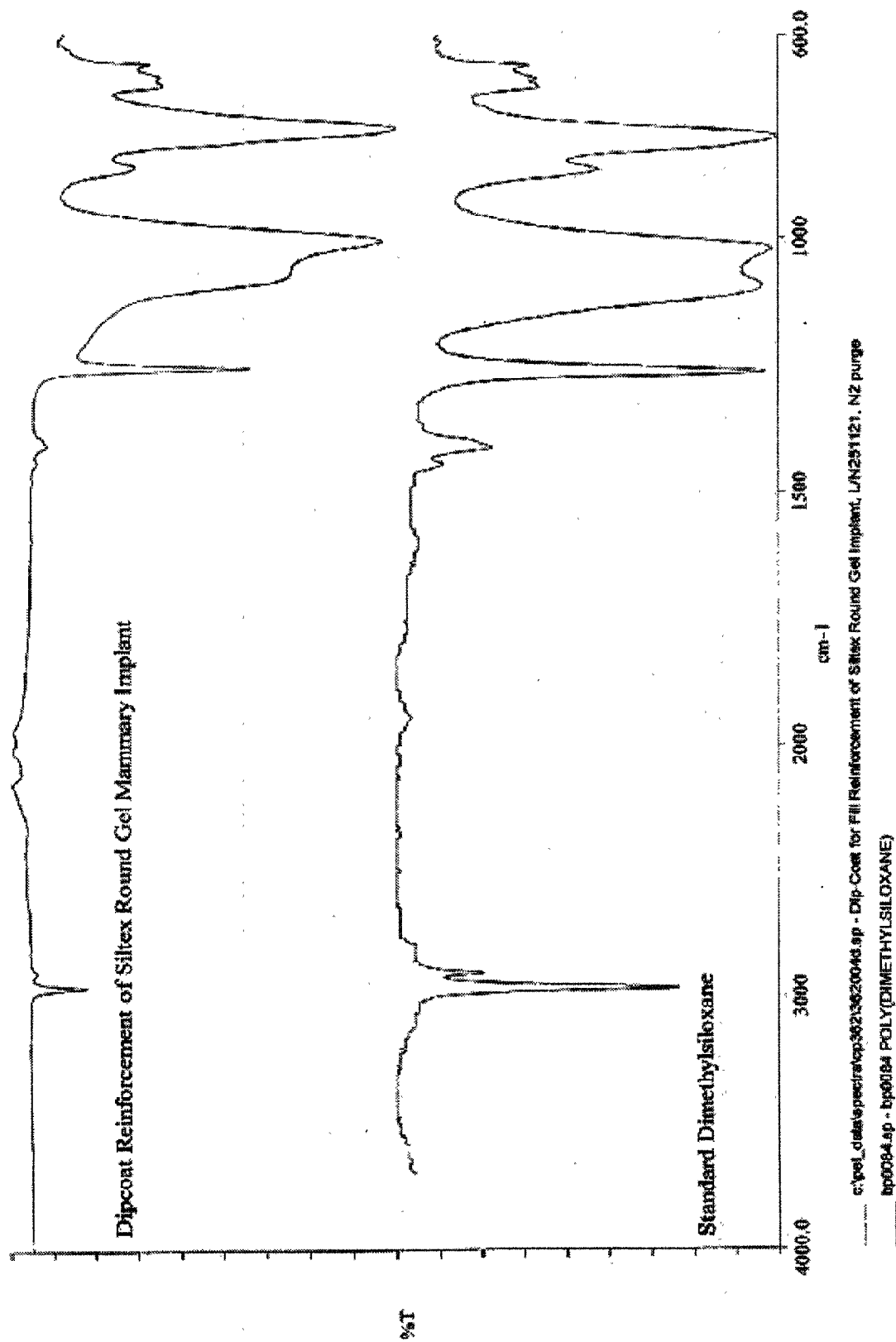


Figure 5-4. IR Spectra Overlay of Dipcoat Reinforcement from Siltex Round Gel Mammary Implant and Dimethylsiloxane

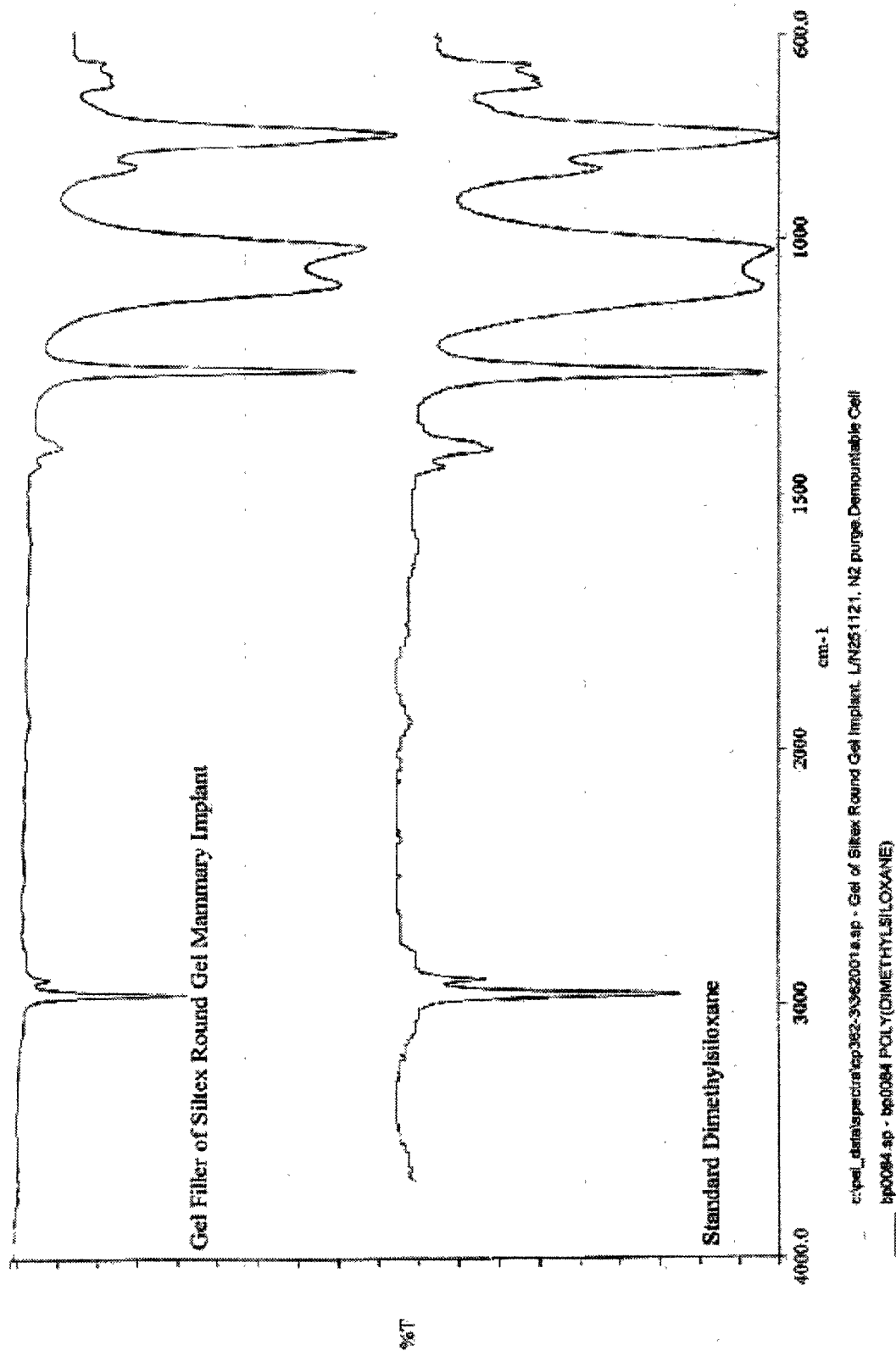


Figure 5-5. IR Spectra Overlay of Gel Filler from Siltex Round Gel Mammary Implant and Dimethylsiloxane

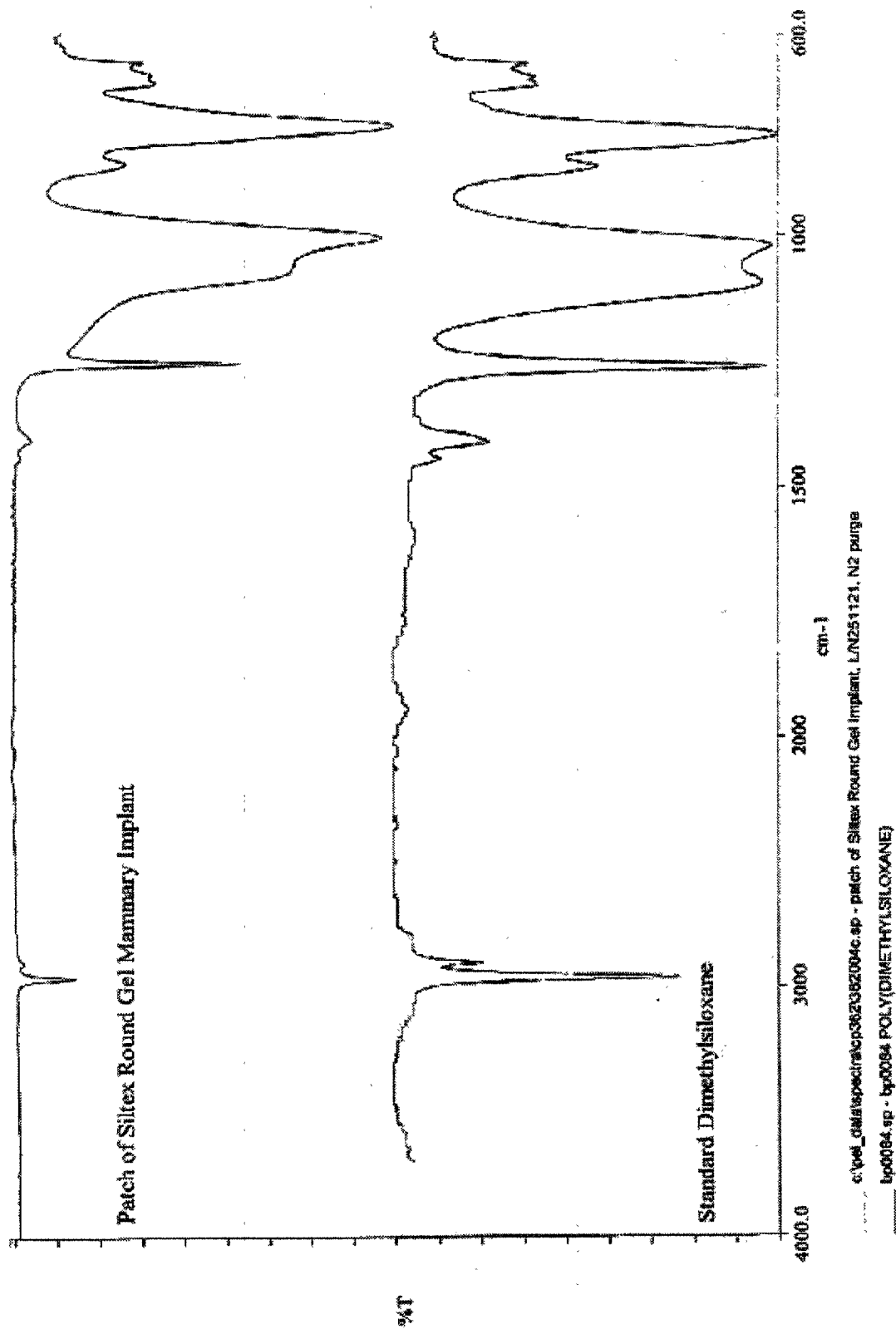


Figure 5-6. IR Spectra Overlay of Patch from Siltex Round Gel Mammary Implant & Dimethylsiloxane

5.8.3 Gas Chromatography / Mass Spectrometry

Liquid extraction followed by gas chromatography/mass spectrometry was conducted to identify and quantify semivolatile extractable compounds from prototype silicone elastomer discs with laser markings versus unmarked control samples. Immersion extractions were performed with methylene chloride at mass of sample to solvent volume ration (M/V) of ~ 1/20 for 1 hour.

Semivolatiles analysis showed no significant differences between the marked samples and controls. No new chemical species were detected and the compounds that were detected (cyclic dimethylsiloxanes, D₄-D₂₂ and solvent residues) were quantitatively similar.

5.8.4 Organic Elemental Analysis

Organic elemental analysis was conducted to determine the concentration of carbon, hydrogen and nitrogen. Samples included silicone elastomer discs with laser marked spots and control.

Organic elemental analysis results obtained from silicone elastomer discs that were laser marked (three (3) and nine (9) laser passes) and unmarked control samples are shown in Table 5-13. Nitrogen, carbon and hydrogen percentages are indistinguishable for the control and the laser marked spots. Further, no differences were observed for the three (3) and nine (9) laser passes.

Table 5-13. Organic Elemental Analysis of Laser Marked and Unmarked Silicone Elastomer

Sample Description	Nitrogen (%)	Carbon (%)	Hydrogen (%)
Smooth Silicone Elastomer Disc, Unmarked	<0.02	23.11	5.72
Smooth Silicone Elastomer Disc, Laser Marked, 1 cm Diameter, 3 Passes	<0.02	23.38	5.72
Smooth Silicone Elastomer Disc, Laser Marked, 1 cm Diameter, 9 Passes	<0.02	23.18	5.72

5.8.5 X-Ray Diffractometry

X-ray diffractometry (XRD) was performed to measure amorphous and crystalline silica phases. Samples included silicone elastomer discs with laser marked spots [nine (9) laser passes], unmarked controls, and the reference standards crystalline and amorphous silica. Prototype devices with laser markings were also included for analysis. Standard reference compounds included amorphous and crystalline silica (SiO₂).

Two prominent diffraction patterns are observed for the laser marked and control samples. The abundance of this pattern is more prominent for the laser engraved spot. This may be attributable to increased silica exposure. The diffraction pattern corresponding to crystalline silica yields narrow diffraction patterns at a unique position on the spectra. The characteristic pattern for crystalline silica is absent from laser-marked and control sample. Accordingly, no crystalline silica is present prior to and following laser engraving. Prototype devices did not show any differences when analyzed with XRD.

5.8.6 X-Ray Photoelectron Spectroscopy

X-ray photoelectron spectroscopy (XPS) was undertaken to determine atomic percentage chemical composition of the surface for carbon, nitrogen, silicon and oxygen. Samples included silicone elastomer discs with laser marked spots and unmarked controls. Prototype devices with laser markings were also examined. Standard reference compounds included amorphous silica, carbon and silicon carbide.

X-ray photoelectron spectroscopy (XPS) results were obtained on laser marked silicone elastomer discs (marked with a spot, none (9) laser passes) and a control with no marking. Refer to Table 5-14 for results of the analysis. (Similar results were obtained for the prototype devices.) Binding energies typical of polysiloxane bonds were observed. Carbon atomic percentage decreases for the laser engraved spot and oxygen and silicon increase. This may be attributable to an increase of exposed silica filler in the laser engraved spot. An additional qualitative analysis was performed and confirmed an apparent increase in silica content at the laser engraved markings.

Table 5-14. XPS Elemental Analysis of Laser Marked and Unmarked Silicone Elastomer

Sample Description	Atomic Percentage		
	Carbon (%)	Oxygen (%)	Silicon (%)
Smooth Silicone Elastomer Disc, Unmarked	52.6	27.7	21.6
Smooth Silicone Elastomer Disc, Laser Marked 1 cm Diameter 9 Passes	35.8	39.9	24.3

5.8.7 Raman Spectroscopy

Raman spectroscopy was utilized to determine organic molecular chemical composition. Samples included silicone elastomer discs with laser marked spots [nine (9) passes] and controls. Prototype devices with laser engraved marking were also characterized. Standard reference compounds included amorphous silica, carbon, silicon carbide, and vinyl substituted polysiloxane.

The laser marked spot showed an increase in Raman emission at 513 nm that is consistent with a silicon dioxide reference standard. Carbon, vinyl substituted polysiloxane, and silicon carbide compounds were not present.

5.8.8 Conclusions

Extensive characterization of laser marked patches and controls showed that no new chemical species were produced and only amorphous silica filler was detected in the laser marked area. Organic elemental analysis results showed no difference in nitrogen, carbon or hydrogen between laser-marked patches and controls. X-ray photoelectron spectroscopy (XPS) revealed a decrease in carbon and an increase in oxygen and silicon for the laser marked samples versus unmarked ones. This is consistent with the removal of dimethyl siloxane material and the exposure of silica filler. This would be expected in a laser marking process. X-ray diffractometry (XRD) confirmed the enrichment at the surface of laser marked samples. XRD results showed that the exposed silica was amorphous.

5.9 Alternate Mandrel Material Composition

Qualification of an alternate mandrel material for shell dipping was done to permit the use of either mandrel. The original mandrel is made of ----- plastic, which is an unreinforced semi-crystalline thermoplastic based on ----- -- It has high strength and dimensional stability, a high service temperature, a low coefficient of friction, good chemical and abrasion resistance and low moisture absorption. These characteristics make it a good choice for dipping mandrels for HTV silicone shell fabrication. However, ----- material embrittles with age, leading to a build up of stress in the plastic. Occasionally an ----- mandrel shatters during the high temperature exposure of shell curing. When that happens, all the shells making up the lot in that curing stage are discarded.

The alternate mandrel configuration is -----, which has essentially the same service properties as ----- but does not fail due to stress build up. Being hollow, ----- mandrels are lighter in weight than ----- mandrels of equivalent size.

Preliminary qualification of alternate mandrels was done by comparison of the test results from non-gelled shells and shells from finished devices made using the two mandrels. The following tests were performed:

- Total extractable content
- Semivolatile extractable analysis

As part of a final qualification of devices for this PMA submission, finished devices made with not only Teflon-coated stainless steel mandrels but also four other manufacturing changes were fully qualified using the following tests:

- Total extractable content
- Volatiles analysis
- Semivolatile extractable analysis
- Non-volatile extractables analysis
- Sol fraction, equilibrium swell ratio, and crosslink density
- Extractable heavy metals
- Surface FTIR analysis

These data were presented in Sections 5.1 through 5.5 of this Chemical Module submission. Only the extractables and semivolatiles data from the preliminary comparison of shells made from ----- versus ----- mandrels are presented below.

5.9.1 Total Extractable Content

Total extractable content was determined on non-gelled shells and on shells from finished devices.¹⁶ The procedures used were equivalent to those reported in Section 5.2.1 Total Extractables Analysis above. Extractables were determined by sample weight loss. A mass to volume ratio of 1/20 was used with Soxhlet extraction for 20 hours. Results are shown in Table 5-15.

Total extractables for non-gelled shells from ----- mandrels were approximately 0.9% and 1.1% from ----- mandrels. The corresponding amounts for shells from finished devices were 10.2% and 10.3% respectively. The higher result for shells from finished devices is due to diffusion of gel into the shell.

Table 5-15. Comparison of Total Extractables in Shell Assemblies from -----

Mandrel	Nongelled Shell		Shell from Finished Device	
	-----	-----	-----	-----
Device Lot No./Size	232720/350cc	232721/350cc	232720/350cc	231933; 232721/350cc
% Extracted	0.93	1.12	10.19	10.34
% Recovery	98.29	95.83	99.43	98.79

¹⁶ Wenkai Ma, Grace Chiang, Report CP 333, *Total and Semivolatile extractables Analyses of Gel-Filled Mammary Prostheses: ----- Mandrel Qualification*, December 19, 2001.

5.9.2 Semivolatiles Content

Total semivolatiles extractables from non-gelled shells were less than 1200 µg/g from ----- mandrels and less than 1150 µg/g from ----- mandrels. All the compounds reported were below the reliable quantification limit from the method. The analytes detected are shown in Table 5-16 below.

Table 5-16. Comparison of Semivolatile Extractables in Shell Assemblies from ----- (µg/g)

Mandrel	Nongelled S-----		Shell from Finished Device	
	-----	-----	-----	-----
Device Lot No./Size	232720/ 350cc	2-----1/ 350cc	232720/ 350cc	231933,232721/ 350cc
D ₅	ND	ND	<10	<10
D ₁₃	ND	ND	<43	NA
D ₁₄	<107	<106	<121	<120
D ₁₅	<107	<106	<121	<120
-----	<107	<106	<121	<120
-----	ND	<59	ND	ND
-----	NA	<59	ND	ND
-----	<298	NA	<388	<461
-----	NA	<59	ND	ND
-----	<298	<296	<388	<405
-----	ND	<59	ND	ND
-----	<298	<296	<388	<392
Total Semivolatiles (µg/g device)	<1218	<1152	<1583	<1631

5.10 Chemical Characterization Comparison Between Devices Covered by This Submission and Devices Previously Manufactured by Mentor Corporation

Mentor has been manufacturing Low-Bleed Gel-filled Mammary Prostheses since 1985, using silicone raw materials from several vendors. During this time period, one of the largest silicone material vendors (the Dow Corning Corporation) ceased to make their materials available to manufacturers of long-term implantable medical devices, including mammary prostheses.

Consistent with guidance issued by the U.S. FDA regarding replacement of silicone raw material vendors, whenever Mentor incorporated silicone raw materials from a new vendor, extensive comparative raw material testing was performed by those vendors to demonstrate equivalency with the withdrawn products. This testing was carried out in accordance with FDA's "Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials" (July 6, 1993). Such testing included chemical analyses, mechanical testing and short-term biological testing. The results of such testing are included in the vendor's Master Access Files for their materials.

In addition, Mentor itself performed sterile finished product testing using the new vendor materials and compared that chemical data (as well as mechanical data, device manufacturing process information, and short-term biological test results) to previous data from Mentor Gel-filled devices (made with the prior vendor's silicone materials). In particular, Mentor qualified the use of SiTech gel and SiTech shell elastomers in a series of tests performed in 1999 and, previous to that, the use of Applied Silicone Corporation (ASC) gel as a replacement for Dow Corning gel in 1996. All of these qualification tests included a comparison to Dow Corning gel data.

The results of such testing on the raw materials and the finished device mammary prosthesis have demonstrated substantial equivalence per FDA's "Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials,"

In addition to ensuring comparable performance characteristics of the finished sterilized devices, one of the primary purposes of such testing was to also ensure the direct applicability of long-term testing, *i.e.*, chronic toxicity/carcinogenicity, immunotoxicity and reproductive/developmental toxicity, conducted on devices that included previous vendor materials.

The substantial equivalence demonstrated by such testing allows direct application to Mentor's current devices of biological compatibility and toxicological data from Dow Corning and ASC silicone gels and on shells produced from Polymer

Technology Corporation (PTC) that had previously been used in the manufacture of Mentor silicone gel-filled mammary prostheses.

In Section 5.0 (Chemical Analysis) extensive chemical characterization of the current Mentor Low-Bleed Gel-filled Mammary Prostheses based upon SiTech LLC raw materials was presented. This section provides comparable data for Mentor devices that included silicone materials from previous vendors. Test methods validation and testing procedures are described in the original reports and, with one exception, have not substantially changed over the years. The one exception that will be described is the change in the method for determining semivolatiles in extracts, because it was upgraded with new, more sensitive GC/MS equipment and included the addition of standards that allowed for a more accurate silicone compound quantification.

It is important to note that the technology for making the two parts (Parts A and B) which comprise each of the shell silicone dispersions (dimethyl dispersion and ----- dispersion) was transferred from Polymer Technology Corporation to SiTech to ensure the equivalence of the dispersions and final shell characteristics. This means that the processes for producing the intermediates and the specifications for and characteristics of those intermediates (molecular weight, viscosity, etc.) are very similar and that the precise combination of those intermediates into the final formulation is similar.

Comparisons of SiTech, Dow Corning, and ASC gels followed by comparison of SiTech and PTC shells are presented in the following section using the results of the same standard comprehensive chemical testing protocols as were used to characterize the current product. These tests include:

- Volatile content
- Extractable content
- Semivolatile content
- Nonvolatile content
- Extent of crosslinking
- Heavy metal content
- Infrared Spectral Analysis

5.10.1 Volatiles Analysis

5.10.1.1 SiTech, Dow Corning and ASC Gels

The objective of this section is to compare the volatile analysis results of Dow Corning, SiTech gels, and ASC gels. The analysis was

performed as described in Section 5.1 above. The results¹⁷ are presented in Table 5-17.

The results demonstrate that the concentration of volatile components of the SiTech gel are lower than the Dow Corning gel. Most of the material that makes up the volatile content of the gels consists of the cyclic siloxanes D₃ – D₅. The ASC gel contained a higher total volatiles amount compared to the other two gels, however, the volatile compounds extracted were similar to the other devices.

Table 5-17. Volatile Analysis of Dow Corning, SiTech, and ASC Gel

Material	Dow Corning	SiTech	ASC
Report No./Sample ID	CP 276/57535	CP 358/251121	CP 293/169392
Compound	ug/g		
Cyclic Dimethyl Siloxanes			
D ₃	0.7	0.18	72.3
D ₄	0.81	0.49	302.0
D ₅	47.7	1.60	266.5
Miscellaneous Silicon-Containing Compounds			
Methoxytrimethylsilane	0.02	ND	0.11
Dimethoxydimethylsilane	0.02	NA	0.04
MM	ND	ND	ND
MDM	ND	ND	1.35
MD2M	ND	ND	1.62
Vinylheptamethylcyclotetra-siloxane	ND	ND	3.76
Branched Alkane+Siloxane	ND	ND	0.07
Miscellaneous Solvent Residues and Others			
Methyl Butanoate	ND	0.09	ND
Methylene Chloride	0.1	ND	0.36
Xylenes	NA	<0.09	0.52
Nonane	ND	ND	0.13
Decane	ND	ND	0.31
Undecane	1.17	<0.34	0.85
Dodecane	1.85	NA	0.76
Total Volatiles	52.4	2.8	651.3

¹⁷ Grace H. Chiang, Report Number CP 293, *Volatile Extractables Analysis of Gel Mammary Prosthesis: SiTech Raw Material Vendor Qualification*, November 23, 1999.

5.10.1.2 Comparison of Shells from PTC and SiTech Dispersion

The purpose of this section is to compare the volatile content of shells made from raw materials from PTC to that of shells made from SiTech raw materials.¹⁸ The results of analysis of textured, non-gelled shell assemblies from PTC and SiTech are presented in the following table.

Table 5-18. Extractable Volatile Compounds from PTC Shells versus SiTech Shells

Material	NuSil/PTC	SiTech/SiTech
Report No./Sample ID	CP 276/175261	CP 358/251121
Compound	μg/g	
Cyclic Dimethyl Siloxanes		
D3	NA	NA
D4	9.3	<0.06
D5	ND	0.28
Miscellaneous Silicon-Containing Compounds		
Methoxytrimethylsilane ²	2.0	3.13
Methyltriethoxysilane	ND	0.04
Miscellaneous Solvent Residues and Others		
Acetone	ND	1.02
Isopropanol ^{*1}	ND	<1.06
2-Pentanone	ND	0.05
Methyl Butanoate	ND	0.04
4-Methyl-3-penten-2-one	ND	0.07
Xylenes ^{**1}	ND	0.06
Decane ¹	ND	0.09
Benzaldehyde ³	ND	0.04
Undecane ¹	0.67	1.39
Acetophenone ³	ND	0.03
Dodecane ¹	1.1	3.00
Total Volatiles	13.07	10.36

The results show that the total volatiles, 13.1 $\mu\text{g/g}$ for PTC and 10.4 $\mu\text{g/g}$ for SiTech non-gelled shells, are substantially equivalent.

¹⁸ Grace H. Chiang, Report Number CP 293, *Volatile Extractables Analysis of Gel Mammary Implant: SiTech Raw Material Vendor Qualification*, November 23, 1999.

5.10.2 Extractable Content

5.10.2.1 Total Extractables Comparison of Dow Corning, SiTech, and ASC Gel

The objective of this section is to present and compare the results of extractable content testing on Dow Corning, SiTech, and ASC Gel ----- rial. Extractable testing of SiTech gel was reported in ----- of this module, but is also presented here for comparison ----- 19. The testing of Dow Corning gel was carried out and reported in 1999.¹⁹

**Table 5-19. Total Extractables from SiTech, Dow Corning, and ASC Gel
(Gel From Siltex Gel-filled Device)**

Gel Vendor	Dow Corning	SiTech	ASC
Report No./Sample ID	CP275I/ 275004-6	CP 358/251121	CP275I/275007-9
%Total Extractable (Wt Loss)	85	83	81

*Wt loss at Exhaustiveness - When the level of the analyte for the nth successive extraction is less than one-tenth (< 0.1) of the first extraction.

NA - not available

Exhaustive extraction of Dow Corning, SiTech, and ASC gel samples produce substantially equivalent results, from approximately 81% to 85% weight loss. Variability in the range reported is typical for handling and testing samples with the characteristics of silicone gel.

5.10.2.2 Total Extractable Content Comparison of Shells from PTC and SiTech Dispersion

The objective of this section is to present and compare the results of extractable content testing on samples of shells from finished product made from PTC and from SiTech dispersion. The patches and the texture layer on Siltex products are made either from NuSil ----- or from SiTech ----- . Extractable testing of SiTech shell material is presented here²⁰ with that for PTC shell material in Table 5-20. The testing of PTC materials was carried out and reported in 1999.²¹

¹⁹ C. S. Puckett, Report Number CP 290, *Total Extractables Analysis of Gel-Filled Mammary Prostheses: SiTech Raw Material Vendor Qualification*, December 2, 1999.

²⁰ Grace H. Chiang, Report Number CP 357, *Total and Semivolatile Extractables Analyses of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, January 16, 2003.

²¹ C. S. Puckett, Report Number CP 290, *Total Extractables Analysis of Gel-Filled Mammary Prostheses: SiTech Raw Material Vendor Qualification*, December 2, 1999.

Table 5-20. Comparison of Total Extractable Results from Shell Assemblies Made with Materials from Different Vendors

Material Vendor (Report #)	Device Siltex Shell			Non-gelled Siltex Shell		
	NuSil/ PTC* (CP275)	NuSil/ SiTech** (CP290)	SiTech/ SiTech*** (CP357)	NuSil/ PTC* (CP275)	NuSil/ SiTech** (CP290)	SiTech/ SiTech*** (CP357)
% Total Extractables	14.34	12.52	10.43	1.42	1.66	1.86

* - NuSil/PTC = NuSil ----- sheeting with PTC shell

** - NuSil SiTech = NuSil ----- sheeting with SiTech shell

*** - SiTech/SiTech = SiTech ----- sheeting with SiTech shell

The data in the chart demonstrates that the total extractable content is not substantially different for non-gelled shells made from PTC and SiTech raw materials. The total ranges from 1.42% to 1.86%. It is also evident that the results are not influenced by use of NuSil or SiTech ----- material for the textured sheeting.

For shells from finished product, the extractable content ranged from 10.43% to 14.34%. The source of the larger extractable amount and greater variability compared to non-gelled shells are the result of exposure to gel and diffusion of some of the gel into the shell, as well as the variability in sample preparation in removal of gel from the surface of the shell.

The results demonstrate that shells made from PTC elastomer and those made from SiTech elastomer are not substantially different. The results also demonstrate that there is no substantial difference between shells with a textured layer made from NuSil material and shells with a textured layer from SiTech material.

5.10.3 Semivolatile Content of Extractables

Semivolatile analysis involves the determination of the concentration of compounds with molecular weights of up to 1500 Daltons in the solvent extractables from a sample (gel filler or shell). Due to the potential concern of the FDA related to lower molecular weight siloxanes, and in particular octamethylcyclotetrasiloxane (D₄), Mentor has worked with its vendor, SiTech LLC, over the past two years to reduce this and other homologous compounds in the intermediates for the production of gel-filled implants, with particular emphasis on gel precursors since the gel component comprises the bulk of the implant structure. This reduction is accomplished through

stripping under high vacuums of gel polymer raw materials. This process reduces the concentrations of compounds in relation to their vapor pressure. For a homologous series, such as cyclic siloxanes, vapor pressure is inversely proportional to their molecular weight, i.e., the lower the molecular weight, the higher the vapor pressure. This means that the lower the molecular weight the greater will be the reduction in final concentration. Thus, in a thoroughly stripped intermediate, D₄ will have the lowest concentration, D₅ the next highest, D₆ higher than D₅ and so forth as the molecular weight within the cyclic series increases. The same relationship will apply to the homologous linear series: MM, MDM, MD2M, etc.

Siloxane polymers that are the raw materials in the fabrication of gel-filled mammary implants are formed through equilibration reactions from mixtures of endblocker (MM) or modified endblocker ($M^{Vi}M^{Vi}$), cyclic dimethyl siloxanes (D₄, D₅, D₆, etc.) and modified cyclic siloxanes, such as D₄^{Vi} or D₄^{Ph}. These reactions are catalyzed by strong acids or bases. At the completion of the equilibration reaction, the acid is eliminated, thus stabilizing the polymer. This equilibrium mixture contains from 12 to 15 weight percent low molecular compounds, most of which are cyclic compounds. The preponderance of the light materials is D₄. It accounts for about 50 weight percent of the light species formed during equilibration. After the equilibration catalyst is eliminated, these species can be stripped from the mixture under high vacuum and elevated temperature. If the catalyst is not effectively eliminated, low molecular weight compounds will continue to be created with the result that it would be very difficult to maintain a high vacuum and, as these compounds are removed, the molecular weight of the polymer will decrease. The fact that SiTech is able to strip the polymers provided to Mentor to very low levels is proof that the catalyst has been removed and that the polymer is stable and that no light materials, low molecular weight cyclic siloxanes, will be regenerated in the polymer during further processing into an implant.

5.10.3.1 Change in Semivolatiles Method of Analysis

Over the past two years Mentor has significantly enhanced its capabilities for semivolatile extractables analysis by the addition of new gas chromatography/mass spectrometer (GC/MS) equipment and the use of additional cyclic dimethylsiloxane standards in the analysis method.²²

The replacement of a Hewlett Packard Model 5890/5971 with an Agilent 6890 plus 5973N resulted in an increase in the capability to detect low level compounds by factors of from 1.5 to 37, depending

²² Grace H. Chiang, Report Number CP 351, *Semivolatile Extractables Analysis of Gel Mammary Implant: Comparison of Instruments and Quantitation Methods*, January 14, 2003.

upon the specific compound. The effects of the increased sensitivity are more pronounced for late-eluting (higher molecular weight) compounds. Simply stated, this means that the analysis using this new equipment would include compounds that could not formerly be detected, especially as the molecular weight approaches 1500 Daltons.

The introduction of additional standards of higher cyclic dimethylsiloxanes (D₁₅, D₁₈, and D₂₁) resulted in more accurate quantification for compounds in the range of D₁₄-D₂₁.

The change in standards and GC equipment resulted in a more precise and accurate capability to detect and quantify silicone extractables, especially those with molecular weights closer to 1500 Daltons. The improvements, however, have made the direct comparison of earlier semivolatiles data to current data problematic at times.

A project was undertaken and completed to identify and, where possible, to quantify the differences that resulted from the previous and newer analytical techniques. Report CP 351 documents a comparative study of the two analytical techniques that included changing the GC/MS instrument and adding the additional standards for the quantification of cyclic siloxanes.

The study samples included Mentor Siltex Round Moderate Gel Implants that have been analyzed previously by the original GC/MS instrument and quantified with the use of then-available standard cyclic dimethylsiloxanes (D₃, D₄, D₅, D₆, D₉, and D₁₂). For the comparative study, the same methylene chloride Soxhlet extraction procedure as was used in prior studies was employed.

The extractions were conducted on device components (gel filler and shell assembly) rather than whole devices. Total extractables were determined gravimetrically following the evaporation of methylene chloride. Total extractables of gel samples were the same (78 weight % from Report Number CP 290, July, 1999 vs. 81 weight % from Report Number CP 351, July, 2002) for the old and new analytical methods.

The semivolatiles present in the extracts were analyzed by both the older and newer analytical techniques through direct liquid injection. The component peaks were identified based on their retention indices, and spectra matched against library reference compounds. Quantitative results were obtained using the same internal and

external calibration methods with and without the inclusion of the additional standards D₁₅, D₁₈, and D₂₁.

The change of quantitation method affected the results of D₁₄-D₂₁. Previously, the quantitation of these dimethylcyclsiloxanes was based upon the calibration factor of D₁₂ as the standard. This resulted in an underestimation of the values for the higher dimethylcyclsiloxanes since the response factor based upon D₁₂ provided inaccurately low results for compounds where the number of dimethyl siloxane units significantly exceeded that of D₁₂. As expected, when additional calibration standards (D₁₅, D₁₈, and D₂₁) were used to quantify D₁₄-D₁₆, D₁₇-D₁₉, and D₂₀-D₂₁, respectively, significant increases in values were observed. Table 5-21 is abstracted from the data presented in Tables II and III of Report CP 351.²³ The old GC equipment utilizing both the old and new calibration standards was used to demonstrate the improved quantification of siloxane compounds. The analyses were conducted at the same time. Figure 5-7 is a plot of the data on gel filler. When using the same GC with the old and new sets of standards the results up through D₁₃ match exactly. For D₁₄-D₁₇ the values from the two calibration schemes digress. Values from D₁₇-D₁₉ decrease but are still above the values for the old calibration scheme. D₂₀ and D₂₁ for the new calibration standards are at non-detectable levels.

Recall from the analysis of stripping, presented above, that the values for a homologous series should increase in a stripped polymer. We can conclude from this that the new calibration standards more accurately define the cyclic dimethylsiloxane content of the material. However, it appears that the older instrument is not as capable of accurately detecting (sensitivity) species above D₁₉ and the sensitivity is decreasing from D₁₇ upward. Since the same sample was analyzed utilizing both the original and newer set of standards, the same concentration of the cyclic materials must be present. Since the analysis with the new standards most closely matches the concentration of homologous compounds that must be present, one can conclude that the new standards provide a more accurate accounting of the composition of the stripped polymer. The critical conclusion, in terms of comparing previous and newer analyses on different materials utilizing the previous and newer standards is that, if there is a good match of concentrations of dimethyl compounds up through D₁₂ to D₁₃, then the two materials will be similar if not identical in cyclic dimethyl content, both for individual species and for the cumulative total.

²³ Grace H. Chiang, Report Number CP 351, *Semivolatile Extractables Analysis of Gel Mammary Implant: Comparison of Instruments and Quantitation Methods*, January 14, 2003.

The linear dimethyl siloxanes in extracts from the same gel analyzed with the same GC and the two standards produced very similar results with a difference of $<0.6 \mu\text{g/g}$ for any specific compound (MD_{12}M - MD_{15}M). See Table 5-21. Note that the total semivolatiles from the application of the new standards to extracts from gel samples increased from 0.16 to 0.42 weight %. This increase was due solely to the more accurate determination of cyclic dimethyl siloxanes. Note also that, other than cyclic and linear dimethyl siloxanes, no other compounds were detected in the extractables from the gel sample.

The increased sensitivity in the cyclic dimethylsiloxane analytical results when the new GC instrument and additional standards are used to analyze gel filler solvent extractables can be seen in Figure 5-7. The only difference when this comparison is made is that of the sensitivity of the two instruments. Results on cyclic dimethylsiloxanes up through D_{10} are nearly identical. From D_{12} through D_{18} , the new instrument is capable of detecting lower levels than the original GC instrument. From D_{18} through D_{21} the results from the original instrument decrease rapidly to nondetectable values at D_{20} and D_{21} while the values provided by the new instrument and standards remain in the 500 to 800 $\mu\text{g/g}$ range. In a stripped polymer, the concentration of the higher molecular weight cyclic siloxanes would be expected to remain at these levels; therefore, it can be concluded that the new instrument provides a more accurate profile of the cyclic dimethylsiloxanes.

The improved sensitivity of the new GC instrument for linear dimethylsiloxanes is clearly evident in Figure 5-8. Analyses from the old instrument do not show any linear dimethyl siloxanes up through MD_{11}M , while results from the new instrument show an increasing concentration from MD_5M through MD_{13}M . This would be the expected result in a stripped polymer. The new chromatograph also detects linear materials in the MD_{16}M - MD_{17}M range while the older instrument is not sensitive enough to detect any material in this range.

Further proof of the superior sensitivity of the new instrument comes from the fact that it detects and quantifies cyclic vinyl-modified siloxanes in the range of D^{Vi}_9 - $\text{D}^{\text{Vi}}_{21}$ while the old instrument does not. With the excess of vinyl-modified polymer in the gel precursor formulation, these materials must be present in the final gel. Thus, it is concluded that the new gas chromatograph coupled with the new calibration standards provide more accurate results than the old method and that those results will accurately reflect the expected profiles of the various species in the implant.

For emphasis, the point must be reiterated that, if the results on cyclic dimethylsiloxanes are essentially identical for D₄ through D₁₁, then it can be concluded that the stripped polymers upon which the analyses were conducted will be essentially identical with regard to trace siloxanes.

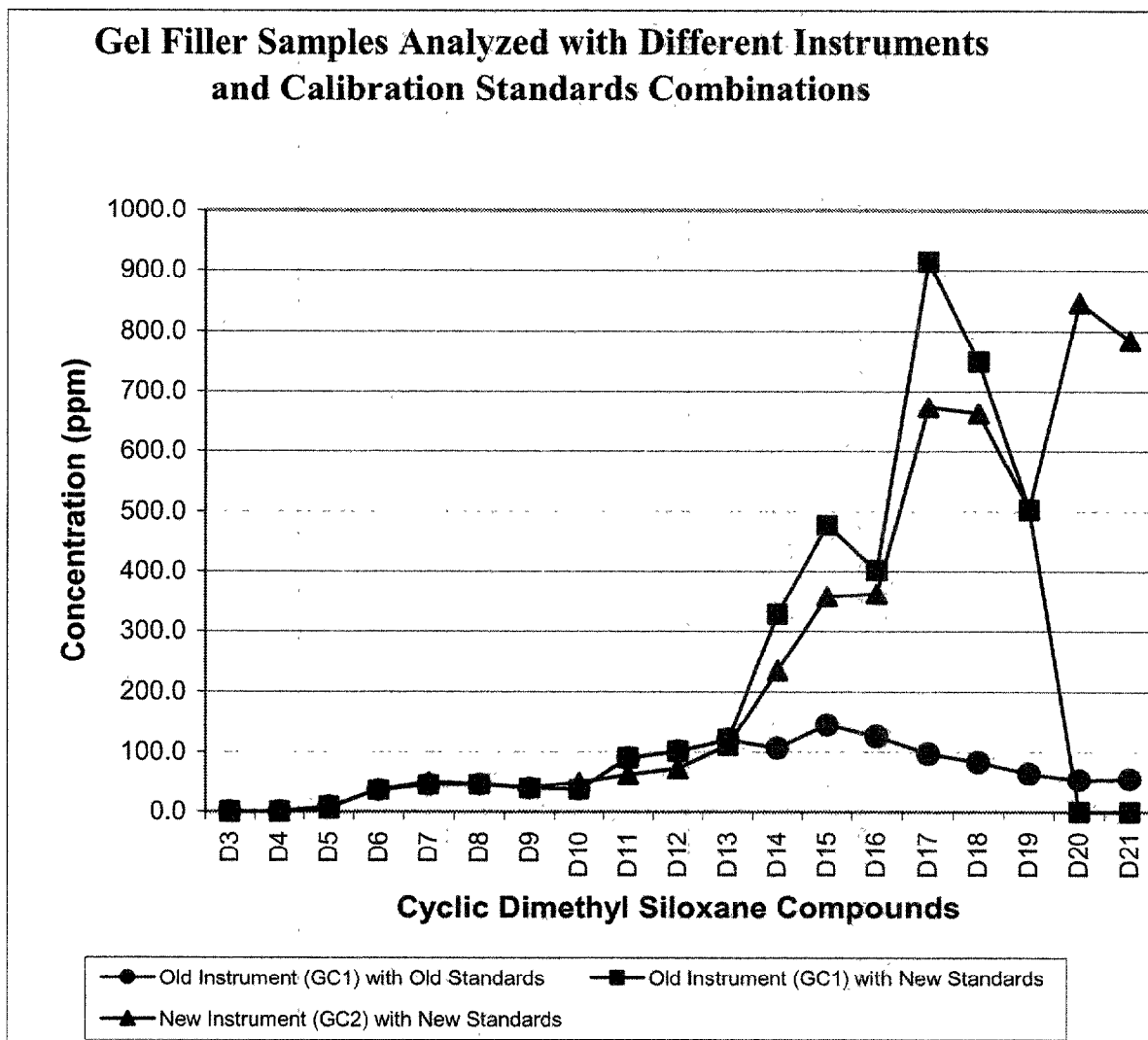


Figure 5-7. Comparison of Analytical Results on Cyclic Dimethyl Siloxane in Gel Filler Samples as determined by Old GC Instrument Employing Original and Additional Calibration Standards and New GC Instrument Employing Additional Calibration Standards

Table 5-21. Semivolatile Extractables from Siltex Round Moderate Profile Gel-Filled Mammary Implants (Lot #188747) - Different Gas Chromatographs and Calibration Standards (CP351)

Method of Calibration	Old Instrument (GC1) plus Original Calibration Standards 1		Old Instrument (GC1) plus New Calibration Standards 2		New Instrument (GC2) plus New Calibration Standards 2	
	Gel Filler	Shell	Gel Filler	Shell	Gel Filler	Shell
Compound	ug/g					
CYCLIC DIMETHYL SILOXANES						
D ₃ ¹	ND	ND	ND	ND	ND	ND
D ₄ ¹	ND	ND	ND	ND	NA	ND
D ₅ ¹	8.0	ND	8.0	ND	6.0	3.3
D ₆ ¹	36.8	34.4	36.8	34.4	38.2	32.5
D ₇ ²	45.2	<31.8	45.2	<31.8	50.5	32.5
D ₈ ²	45.9	<72.2	45.9	<72.2	47.7	27.4
D ₉ ¹	39.8	<72.2	39.8	<72.2	41.5	24.7
D ₁₀ ²	37.7	<72.2	37.7	<72.2	49.7	25.7
D ₁₁ ²	90.5	<98.5	90.5	<98.5	63.1	47.8
D ₁₂ ¹	101.4	<98.5	101.4	<98.5	73.3	63.9
D ₁₃ ²	120.6	<98.5	120.6	<98.5	111.8	90.3
D ₁₄ ²	107.0	<98.5	328.7	<436.6	234.8	194.5
D ₁₅ ¹	145.5	<98.5	476.9	<436.6	357.7	217.7
D ₁₆ ²	126.1	<100.8	401.7	<436.6	361.8	215.7
D ₁₇ ²	97.5	<98.5	914.2	<818.1	672.4	379.2
D ₁₈ ¹	83.6	<98.5	748.7	<818.1	662.1	297.2
D ₁₉ ²	64.4	<98.5	502.2	<818.1	503.7	369.3
D ₂₀ ²	53.6	<98.5	NA	ND	845.7	456.9
D ₂₁ ¹	55.4	ND	NA	ND	784.3	505.5
LINEAR DIMETHYL SILOXANES						
MDM ¹	ND	ND	ND	ND	ND	ND
MD ₂ M ¹	ND	ND	ND	ND	ND	ND
MD ₃ M ¹	ND	ND	ND	ND	ND	ND
MD ₄ M ¹	NA	ND	NA	ND	<0.77	NA
MD ₅ M ¹	NA	ND	NA	ND	NA	ND
MD ₆ M ¹	<5.56	ND	<5.56	ND	2.5	<4.7
MD ₇ M ¹	NA	ND	NA	ND	4.9	<5.00
MD ₈ M ¹	<14.03	ND	<14.03	ND	8.6	<5.3
MD ₉ M ¹	<20.7	ND	<20.69	ND	16.2	9.2
MD ₁₀ M ¹	<19.0	ND	<18.99	ND	25.7	16.1
MD ₁₁ M ²	NA	ND	NA	ND	40.6	21.6
MD ₁₂ M ¹	88.4	ND	89.0	ND	73.3	53.3
MD ₁₃ M ²	86.5	ND	86.8	ND	89.7	57.1
MD ₁₄ M ²	78.1	ND	78.3	ND	87.6	63.0
MD ₁₅ M ²	63.0	ND	63.2	ND	95.0	57.6

Method of Calibration	Old Instrument (GC1) plus Original Calibration Standards 1		Old Instrument (GC1) plus New Calibration Standards 2		New Instrument (GC2) plus New Calibration Standards 2	
	Gel Filler	Shell	Gel Filler	Shell	Gel Filler	Shell
Compound	ug/g					
MD ₁₆ M ³	ND	ND	ND	ND	75.5	48.3
MD ₁₇ M ²	ND	ND	ND	ND	33.6	39.8
CYCLIC VINYL MODIFIED SILOXANES						
D ^{VI} D ₉ ^{2,4}	ND	ND	ND	ND	1.2	ND
D ^{VI} D ₁₀ ^{2,4}	ND	ND	ND	ND	1.5	ND
D ^{VI} D ₁₁ ^{2,4}	ND	ND	ND	ND	NA	ND
D ^{VI} D ₁₂ ^{2,4}	ND	ND	ND	ND	3.7	NA
D ^{VI} D ₁₃ ^{2,4}	ND	ND	ND	ND	6.8	<8.52
D ^{VI} D ₁₄ ^{2,4}	ND	ND	ND	ND	11.5	13.7
D ^{VI} D ₁₅ ^{2,4}	ND	ND	ND	ND	15.2	17.9
D ^{VI} D ₁₆ ^{2,4}	ND	ND	ND	ND	18.3	20.2
D ^{VI} D ₁₇ ^{2,4}	ND	ND	ND	ND	45.0	<31.1
D ^{VI} D ₁₈ ^{2,4}	ND	ND	ND	ND	42.1	<36.5
D ^{VI} D ₁₉ ^{2,4}	ND	ND	ND	ND	33.9	37.9
D ^{VI} D ₂₀ ^{2,4}	ND	ND	ND	ND	69.9	<144.4
D ^{VI} D ₂₁ ^{2,4}	ND	ND	ND	ND	67.5	<144.4
MISCELLANEOUS SILOXANES*						
Siloxane ³	NA	ND	NA	ND	NA	NA
Siloxane ³	ND	ND	ND	ND	1.0	NA
Siloxane ³	ND	ND	ND	ND	ND	NA
Siloxane ³	ND	ND	ND	ND	4.2	1.2
Siloxane ³	ND	ND	ND	ND	1.9	1.1
Siloxane ³	ND	ND	ND	ND	6.9	2.2
Siloxane ³	ND	ND	ND	ND	ND	1.3
Siloxane ³	ND	ND	ND	ND	3.5	1.8
Siloxane ³	ND	ND	ND	ND	ND	NA
Siloxane ³	ND	ND	ND	ND	4.1	1.7
Siloxane ³	ND	ND	ND	ND	6.2	NA
MISCELLANEOUS COMPOUNDS						
Dodecane ³	ND	ND	ND	ND	ND	1.7
Ester ³	ND	ND	ND	ND	ND	1.3
Ester ³	ND	ND	ND	ND	ND	2.4
Tetradecane ³	ND	ND	ND	ND	ND	0.9
Phenol derivative ³	ND	ND	ND	ND	ND	NA
Pentadecane ³	ND	ND	ND	ND	ND	NA
Ester ³	ND	ND	ND	ND	ND	1.3
Dibutyl Phthalate ¹	ND	ND	ND	ND	ND	NA

Method of Calibration	Old Instrument (GC1) plus Original Calibration Standards 1		Old Instrument (GC1) plus New Calibration Standards 2		New Instrument (GC2) plus New Calibration Standards 2	
	Gel Filler	Shell	Gel Filler	Shell	Gel Filler	Shell
	ug/g					
Amide ³	ND	ND	ND	ND	ND	2.5
Di (Ethylhexyl) Phthalate ¹	ND	ND	ND	ND	ND	<4.7
Total Unidentified	ND	ND	ND	ND	1.0	3.8
Total Semivolatiles	1634.3	1269.9	4215.6	4342.3	5803.6	3847.1

ND = Not Detected, S/N <3.0

NA = Not Applicable, at least one of the replicates had a ND value.

Data preceded with a "<" symbol meaning a less than method detection limit value.

*Miscellaneous siloxanes differ based upon retention time (i.e., molecular weights)

¹ Measurement based on external and internal standard calibrations.

² Due to unavailability of external standards, measurement is estimated, based on calibrated response factors of closest homologue.

³ Measurement based on the response factor of closest internal standard.

⁴ Tentative identification based on MS pattern.

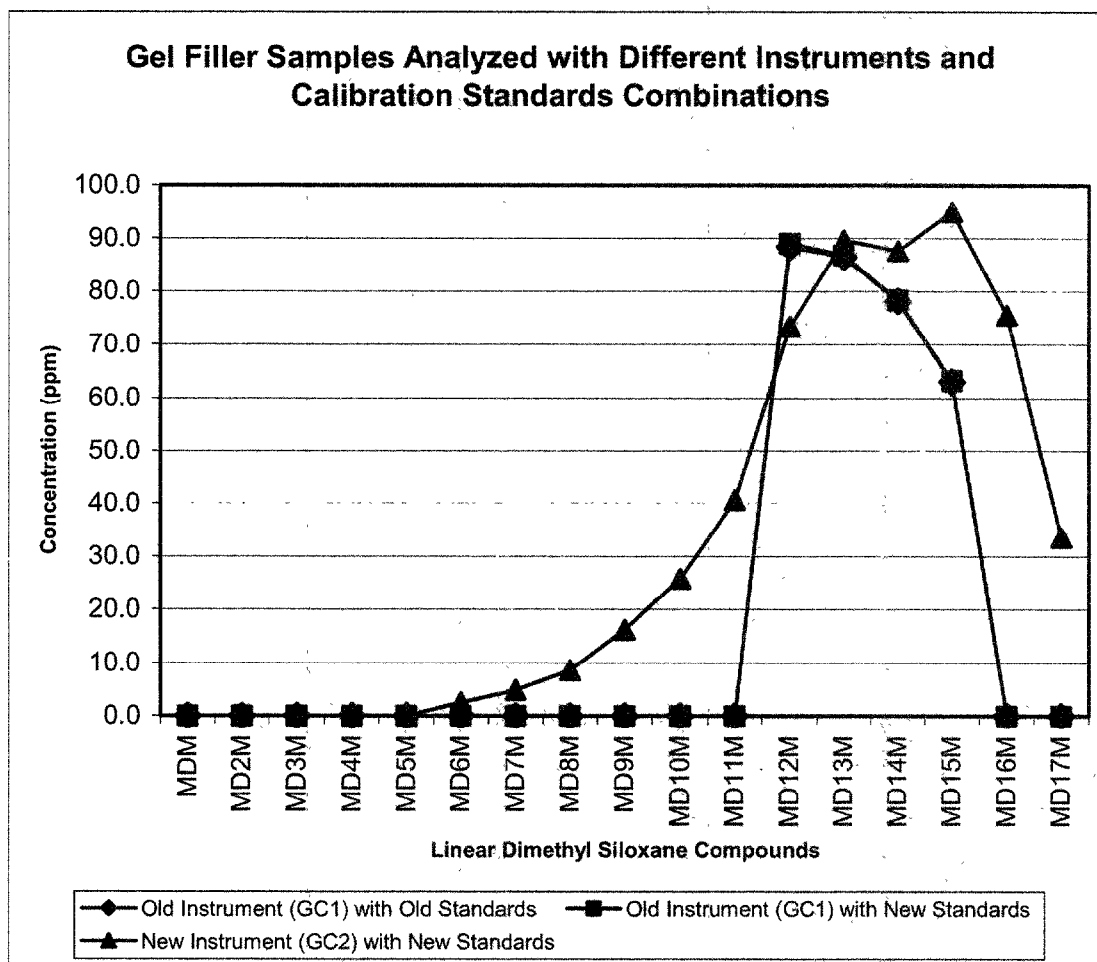


Figure 5-8. Comparison of Analytical Results on Linear Dimethyl Siloxane Compounds in Gel Filler Samples as determined by Old GC Instrument with Original and New Calibration Standards and New Instrument with Additional Calibration Standards

5.10.3.2 Semivolatiles Comparison of Dow Corning, SiTech, and ASC Gel

The objective of this section is to compare the analysis of low molecular weight methylene chloride Soxhlet extractables from Dow Corning, SiTech, and ASC gel filler material using Mentor's GC/MS techniques. Testing of SiTech gel is reported above in Section 5.2.2.²⁴ and is presented again here for comparison in Table 5-22. Earlier testing of SiTech gel, along with testing of Dow Corning and ASC gel, was reported in 1999.²⁵

The change in methodology relating to the use of higher molecular weight standards was explained above. The effect can be noted here in the results from Report Number CP 357 compared to the earlier results. The use of improved standards and more sensitive instrumentation give more accurate quantification of the higher molecular weight species.

The concentration of cyclic dimethylsiloxanes with molecular weight up to approximately 1500 (D₃-D₂₁) for SiTech gel is 3804 µg/g for the recent results compared to 1630 µg/g for the method using the previous standards. The corresponding Dow Corning and ASC gel results from the earlier analysis are 1071 and 3020 µg/g, respectively. As explained above, the concentration of higher molecular weight species in the results of the more recent analysis is a more accurate representation of the cyclic content from D₁₄ – D₂₁ in the material. The corresponding values for D₁₄ – D₂₁ in SiTech gel for more recent versus earlier results are 3649 µg/g and 1089 µg/g respectively. The results for Dow Corning and ASC gels from the earlier analysis are 448 and 728 µg/g, respectively.

The results of the lower cyclic compounds D₃ – D₅ are 40, 35, and 191 µg/g for SiTech, Dow Corning, and ASC gels, respectively, from the earlier analysis, and 3 µg/g for SiTech gel from the more recent, improved analysis. For D₄, the result for the two analyses of SiTech gel was 0.5 µg/g or less. The D₄ results for Dow Corning and ASC are 11.7 and 81.4 µg/g, respectively.

²⁴ Grace Chiang, Report CP 357, *Total and Semivolatile Extractables Analyses of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, dated January 16, 2003.

²⁵ Grace H. Chiang, Report Number CP 292, *Semivolatile Extractable Analysis of Gel-Filled Mammary Prostheses: SiTech Raw Material Vendor Qualification*, November 22, 1999.

For D₃ – D₁₁ the results are 69 µg/g for SiTech (newer assay method) and 295, 449, and 2011 µg/g for SiTech, Dow Corning, and ASC respectively (older assay method).

The corresponding amounts of linear dimethylsiloxanes (MDM-MD₁₇M) in SiTech gel are 376 µg/g and 328 µg/g. The values for linears from Dow Corning and ASC gel are 307 and 767 µg/g respectively.

The comparison of low molecular weight ("semivolatile") extractable compounds from Dow Corning and SiTech gels shows that the total amounts by the earlier method are similar at 1378 µg/g compared to 2525 µg/g respectively. (Note that about 500 µg/g of SiTech's 2525 µg/g semivolatile extractables were barely detectable and therefore only quantifiable by assigning a concentration of less than their detection limits). The amount of linear siloxanes in each data set is equivalent. The amount of D₄ and the total amount of low molecular weight cyclics D₃ – D₁₁ in SiTech gel are equivalent (about the same or less) than the corresponding amounts in Dow Corning gel. By the recent analytical procedure, the low molecular weight extractable content of SiTech gel is 4350 µg/g. From the result of the analysis of the SiTech gel by the recent improved analytical procedure compared to the results of the earlier procedure, and based on the equivalence of the results for lower molecular weight cyclics from both procedures, the profile and amounts of extractables from this analysis demonstrates that the SiTech and Dow Corning materials are not substantially different.

In looking at the semivolatile data for ASC gel, it contains the most semivolatile extractables of all the gels tested by the older method, and more lower molecular weight cyclic extractables (D₃ – D₁₁) than any of the other gels. But, as graphically shown in Figure 5-9, the levels of lower molecular weight cyclic siloxanes from all three gels are more than an order of magnitude below their toxic limit. (Note - the D₄ and D₅ toxicity limits were calculated using the data in the toxicity risk analysis section of this module, Section 6-2; more precisely, by multiplying the cyclic siloxane extractable amount per gram of device by the calculated safety factor for that cyclic siloxane compound. The D₆ through D₁₀ toxicity limits were estimated by multiplying the D₅ toxicity limit by 1.4 to obtain the D₆ limit, the D₆ limit by 1.4 to obtain the D₇ limit, etc. The rationale for using the 1.4 factor to increase the toxicity limit is explained in Section 6.2.2.)

Table 5-22. Semivolatile Extractable Content Comparison of SiTech, Dow Corning, and ASC Gel (using old and current methodologies)

Material (semivol. analysis method)	SiTech Gel (current method)	SiTech Gel (old method)	Dow Gel (old method)	ASC Gel (old method)
Report No./Sample ID	CP 357/251121	CP 292/ 188747	CP 277I/ 57535	CP 277I/ 169392
Compound	ug/g			
Cyclic Dimethyl Siloxanes				
D ₃	ND	ND	ND	5.5
D ₄	0.5	NA	11.7	81.4
D ₅	2.5	40.2	23.6	103.8
D ₆	4.9	ND	76.3	504.5
D ₇	9.0	ND	96.0	677.1
D ₈	8.5	55.8	48.9	236.1
D ₉	8.4	48.1	52.8	142.3
D ₁₀	11.5	49.0	49.5	114.2
D ₁₁	23.3	101.9	89.9	145.9
D ₁₂	35.3	111.8	87.1	138.4
D ₁₃	51.0	134.6	87.6	143.5
D ₁₄	118.7	156.4	76.9	140.5
D ₁₅	181.5	184.3	76.6	135.6
D ₁₆	217.8	163.9	68.4	110.9
D ₁₇	616.4	141.3	62.4	89.8
D ₁₈	560.7	126.4	60.2	76.0
D ₁₉	450.9	108.3	57.0	61.2
D ₂₀	657.8	114.4	46.6	52.4
D ₂₁	845.6	93.9	ND	61.3
Linear Dimethyl Siloxanes				
MDM	ND	ND	ND	ND
MD ₂ M	ND	ND	ND	4.1
MD ₃ M	ND	ND	ND	ND
MD ₄ M	ND	ND	6.5	9.4
MD ₅ M	ND	ND	12.7	18.3
MD ₆ M	ND	ND	25.7	33.6
MD ₇ M	<1.5	ND	27.5	36.4
MD ₈ M	1.7	ND	33.9	41.3
MD ₉ M	3.2	ND	42.2	53.2
MD ₁₀ M	7.2	ND	48.4	60.8
MD ₁₁ M	13.5	ND	44.7	55.9
MD ₁₂ M	37.2	<192.2	65.3	124.8
MD ₁₃ M	54.6	162.3	ND	105.5

Material (semivol. analysis method)	SiTech Gel (current method)	SiTech Gel (old method)	Dow Gel (old method)	ASC Gel (old method)
Report No./Sample ID	CP 357/251121	CP 292/ 188747	CP 277I/ 57535	CP 277I/ 169392
Compound	ug/g			
MD ₁₄ M	66.1	<165.9	ND	84.4
MD ₁₅ M	70	<165.4	ND	82.0
MD ₁₆ M	57.2	165.3	ND	57.6
MD ₁₇ M	64.9	ND	ND	ND
Vinyl-Modified Cyclic Dimethyl Siloxanes				
D ^{vi} D ₁₄	6.8	ND	ND	ND
D ^{vi} D ₁₅	10.1	ND	ND	ND
D ^{vi} D ₁₆	14	ND	ND	ND
D ^{vi} D ₁₇	26.1	ND	ND	ND
D ^{vi} D ₁₈	40.6	ND	ND	ND
D ^{vi} D ₁₉	25	ND	ND	ND
----- Modified Cyclic Dimethyl Siloxanes				
--- --	ND	ND	ND	ND
--- --	21.9	ND	ND	ND
--- --	19.8	ND	ND	ND
--- --	ND	ND	ND	ND
Miscellaneous Siloxanes				
Siloxane	4.2	9.4	ND	ND
Residues of Solvents and Plasticizers				
o-Xylene	<0.4	ND	ND	ND
t-amyl alcohol	ND	34.0	ND	ND
Total Semivolatiles (ug/g)	4350.1	<2525.0	1378.4	3787.7

ND = Not Detected, S/N <3.0

Data preceded with a "<" symbol meaning a less than method detection limit value.

* - isomers

Extractable Cyclic Siloxane Comparison of SiTech, Dow Corning, and ASC Gels (New Versus Old Methodology)

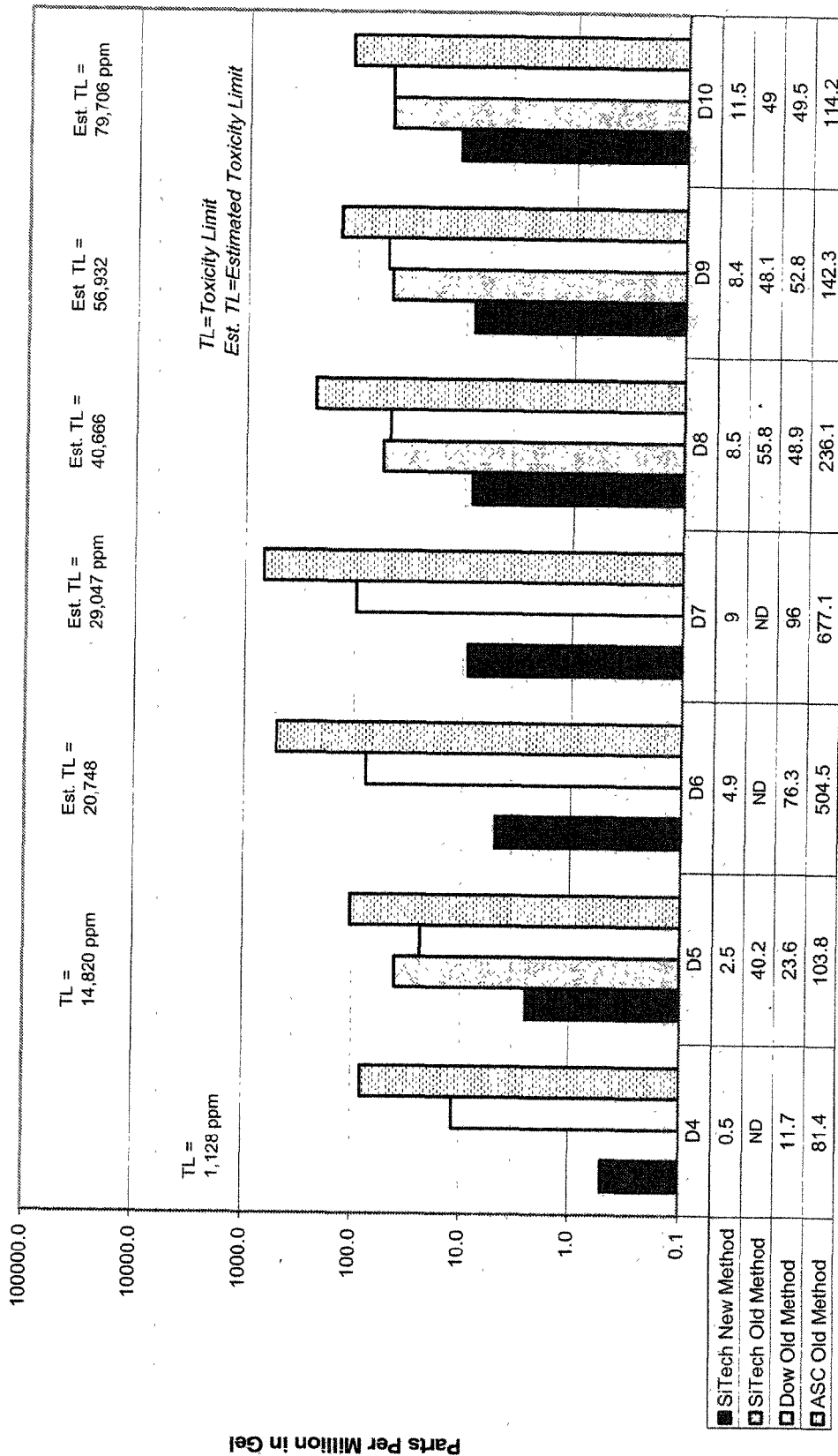


Figure 5-9 Extractable Cyclic Siloxane Comparison of SiTech, Dow Corning, and ASC Gels (New Versus Old Methodology)

5.10.3.3 Semivolatile Extractable Compounds of PTC Elastomer Shells and SiTech Elastomer Shells

The objective of this section is to present and compare the results of analysis of low molecular weight content of methylene chloride extractables performed on non-gelled shells made with PTC elastomer raw materials to those made with SiTech elastomer raw material analyzed by GC/MS technique. The complete reports^{26,27} are appended, and summary data is presented here for comparison in Table 5-23.

The change in methodology relating in the use of higher molecular weight standards was explained above. The effect can be noted here between the results with NuSil textured shells and with SiTech textured shells. The use of improved standards and more sensitive instrumentation give more accurate quantification of the higher molecular weight species.

The comparison of low molecular weight ("semivolatile") extractable compounds, using the older semivolatile method, from NuSil textured PTC shells and SiTech shells shows that the total amount is less than about 2000 µg/g. By the new method, the result for SiTech textured SiTech shells is about 3200 µg/g. These values are not unusual for extractable low molecular weight compounds corresponding to the two different methods of analysis. The amounts are small. The contribution to the low molecular weight extractable compounds of the finished device is very small, given that the weight of the shell is small relative to the total weight of the device.

Cyclics from D₃ through D₁₀ either were not detected or were below the limit of quantification of the method for all the samples. The profile and amounts of extractables from these analyses demonstrate that, for low molecular weight extractable compounds analyzed by GC/MS, the NuSil and SiTech textured layers with PTC and SiTech shells are not substantially different.

²⁶ Grace H. Chiang, Report Number CP 292, *Semivolatile Extractable Analysis of Gel-Filled Mammary Prostheses: SiTech Raw Material Vendor Qualification*, November 22, 1999. Table IIb. The Comparison of Shell Assemblies from Nongelled Siltex Round Low Bleed Gel-Filled Mammary Prostheses.

²⁷ Report CP 357, *Total and Semivolatile Extractables Analyses of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, by Grace Chiang, January 16, 2003. Table II. GC/MS Semivolatiles Analysis of Siltex Round Moderate Profile Gel-Filled Mammary Implants.

Table 5-23. Semivolatile Extractable Content Comparison of PTC and SiTech Nongelled Shells (using old and current methodologies)

Material (Analysis Method)	PTC Shell/NuSil Texture (Old Method)	SiTech Shell/ NuSil Texture (Old Method)	SiTech Shell / SiTech Texture (Current Method)
(Report No./Lot No.)	CP277 II/175261	CP292/194800	CP357/251121
Compound	ug/g		
Cyclic Dimethyl Siloxanes			
D ₃	ND	ND	ND
D ₄	ND	ND	ND
D ₅	ND	ND	ND
D ₆	ND	ND	ND
D ₇	ND	ND	ND
D ₈	ND	ND	<7.8
D ₉	ND	<49	<7.8
D ₁₀	ND	60	<7.8
D ₁₁	ND	118	<12.2
D ₁₂	ND	163	22
D ₁₃	ND	212	49
D ₁₄	73	256	148
D ₁₅	76	267	201
D ₁₆	77	225	207
D ₁₇	ND	159	530
D ₁₈	74	116	388
D ₁₉	72	<86	273
D ₂₀	72	<77	522
D ₂₁	ND	ND	326
Linear Dimethyl Siloxanes			
MDM	ND	ND	ND
MD ₂ M	ND	ND	ND
MD ₃ M	ND	ND	ND
MD ₄ M	ND	ND	ND
MD ₅ M	ND	ND	ND
Vinyl-Modified Cyclic Dimethyl Siloxanes			
D ^{vi} D ₁₄	ND	ND	ND
D ^{vi} D ₁₅	ND	ND	ND
D ^{vi} D ₁₆	ND	ND	ND

Material (Analysis Method)	PTC Shell/NuSil Texture (Old Method)	SiTech Shell/ NuSil Texture (Old Method)	SiTech Shell / SiTech Texture (Current Method)
(Report No./Lot No.)	CP277 II/175261	CP292/194800	CP357/251121
D ^{vi} D ₁₇	ND	ND	ND
----- Modified Cyclic Dimethyl Siloxanes			
--_--_---	ND	ND	<8.9
--_--_---	ND	ND	<8.9
--_--_---	ND	ND	<8.9
--_--_---	ND	ND	85
--_--_---	ND	ND	138
--_--_---	ND	ND	55
--_--_---	ND	ND	<27
Residues of Solvents and Plasticizers			
o-Xylene	ND	ND	ND
Di (Ethylhexyl) Phthalate	ND	ND	<11.2
Chloroform	14.3	ND	ND
Amylene Hydrate	ND	5.6	ND
Total Semivolatiles (ug/g)	458	1794	3167

ND = Not Detected, S/N <3.0

Data preceded with a "<" symbol meaning a less than method detection limit value.

5.10.4 Nonvolatiles Content of Extractables

5.10.4.1 Nonvolatile Content Comparison of Dow Corning Gel, SiTech, and ASC Gel

The objective of this section is to compare the results of molecular weight analysis on methylene chloride Soxhlet extractable content from Dow Corning, SiTech, and ASC gel filler material analyzed by a liquid chromatography (LC) technique [i.e., gel permeation chromatography (GPC)]. Nonvolatile testing of SiTech gel is reported in Section 5.2.3.1 and presented again here for comparison in Table 5-24. The testing of Dow Corning and ASC gel was reported in 1999.²⁸

²⁸ G. Mark Allen, Report Number CP 2781, *GPC Analysis of Nonvolatile Extractables from Gel-Filled Mammary Prosthesis Gel*, May 20, 1999.

Table 5-24. Polysiloxane Molecular Weight Comparison of Dow Corning, SiTech, and ASC Gel Samples by GPC/RI Detector

Report No. (Sample ID)	Device	Mw	Mn	Mw/Mn
Dow Corning Gel (CP 278I/57353)	Siltex Gel-Filled Device	48808	26682	1.8
SiTech Gel (CP 359/251121)	Siltex Gel-Filled Device	53900	22300	2.4
ASC Gel (CP 278I/169392)	Siltex Gel-Filled Device	48926	28310	1.7

Polydimethylsiloxane standards were used for calibration. The molecular weight range from the lowest to the highest is less than 30%. No compounds were detected by LC using UV-Vis detection, which indicates that no -----containing compounds were present at or above the detection limit of the method.

Based on the analysis of nonvolatile content from the Soxhlet extraction procedure, the Dow Corning, SiTech and ASC gels are not substantially different.

5.10.4.2 Comparison of Nonvolatile Extractable Content Between PTC Raw Material Shells and SiTech Raw Material Shells

The objective of this section is to compare the nonvolatile extractable content of shells made from PTC and SiTech raw materials. The results of analysis are presented in Tables 5-25 for shell samples from finished devices and Tables 5-26 for shell samples from non-gelled shells.

Table 5-25. Nonvolatile Compounds in Finished Gel-filled Mammary Prosthesis Shells¹

Tentative Compound Identity	Property	Siltex Round Gel-Filled Shell (100cc, SiTech/SiTech, ² Lot# 251121)	Siltex Round Gel-Filled Shell (100cc, NuSil/SiTech, ³ Lot# 188747)	Siltex Round Gel-Filled Shell (200cc, NuSil/PTC/ASC, ⁴ Lot# 169392)
----- HTV Prepolymer	Mw	ND	71,658	ND
	Mn	ND	56,653	ND
	Mw/Mn	----	1.3	----
----- Polysiloxane	Mw	770	804	ND
	Mn	770	801	ND
	Mw/Mn	1.0	1.0	----
----- Polysiloxane	Mw	550	561	446
	Mn	540	560	444
	Mw/Mn	1.0	1.0	1.0
----- Polysiloxane	Mw	260	293	288
	Mn	250	292	286
	Mw/Mn	1.0	1.0	1.0
----- Polysiloxane	Mw	170	182	141
	Mn	170	181	139
	Mw/Mn	1.0	1.0	1.0
----- Polysiloxane	Mw	ND	ND	82
	Mn	ND	ND	82
	Mw/Mn	----	----	1.0
Polydimethylsiloxane	Mw	17,400	17,596	16,459
	Mn	9,900	14,182	9,359
	Mw/Mn	1.8	1.2	1.8

¹ Reports CP 291 and CP 3-- ND = not detectable

² SiTech/SiTech = SiTe----- SiTech shell and gel

³ NuSil/SiTech = NuSil ----- Tech shell and gel

⁴ NuSil/PTC/ASC = Nu----- /PTC shell/ASC gel

Table 5-26. Nonvolatile Compounds in Nongelled Low-Bleed Shells

Tentative Compound Identity	Property	Siltex Round Shell (100cc, SiTech/SiTech,² Lot# 251121)	Siltex Round Shell (325cc, NuSil/PTC,³ Lot# 175261)
----- HTV Prepolymer	Mw	61,600	91,222
	Mn	49,100	64,232
	Mw/Mn	1.3	1.4
----- Oligomer	Mw	3,900	4,746
	Mn	2,320	2,322
	Mw/Mn	1.7	2.0
----- Polysiloxane	Mw	790	ND
	Mn	780	ND
	Mw/Mn	1.0	----
----- Polysiloxane	Mw	560	448
	Mn	550	445
	Mw/Mn	1.0	1.0
----- Polysiloxane	Mw	290	298
	Mn	280	292
	Mw/Mn	1.0	1.0
----- Polysiloxane	Mw	170	129
	Mn	170	125
	Mw/Mn	1.0	1.0
----- Polysiloxane	Mw	ND	80
	Mn	ND	80
	Mw/Mn	----	1.0
Polydimethylsiloxane	Mw	341,100	ND
	Mn	270,100	ND
	Mw/Mn	1.3	----
Polydimethylsiloxane	Mw	4,820	4,697
	Mn	3,860	3,766
	Mw/Mn	1.2	1.3

¹ Reports CP 278II and CP ----

² SiTech/SiTech = Si----- SiTech shell

³ NuSil/PTC = NuSil -----shell

The results show that the extractables from PTC raw material shells and SiTech raw material shells have extractable compounds of higher molecular weight, between about 50000 and 350000, and polydispersity values not exceeding 2. In addition, similar lower molecular weight compounds are found in both shells and are typical and characteristic of the silicone polymers used as materials of construction. Those compounds of molecular weight less than about 1500 are characterized very thoroughly and in greater detail in Section 5.2.2 (semivolatile extractables analysis). They comprise only a small fraction of the total extractables.

----- containing compounds are detected as a result of extraction from the dimethyl/----- silicone elastomer layer in the shell.

The higher molecular weight compounds comprise the largest fraction of the non-volatile extractables. These are typical and characteristic of the materials of construction. These results demonstrate that the shells made from PTC and SiTech raw materials are not substantially different in their nonvolatiles content.

5.10.5 Extent of Crosslinking, Swell Ratios, and Percent Extractables

5.10.5.1 Extent of Crosslinking Comparison of Dow Corning, SiTech, and ASC Gel

The objective of this section is to summarize and compare the results of analysis of the extent of crosslinking for comparison of gels made with precursor materials from different vendors. The analysis was performed as described in Section 5.3 Sol Fraction Equilibrium Swell Ratio, and Crosslink Density. The values are from samples of gels taken from finished product made with Dow Corning,²⁹ SiTech,³⁰ and ASC gel raw materials. Results are shown in Table 5-27.

Molar crosslink density and crosslink chain density for ASC and SiTech gel are a little higher than for Dow Corning gel. As a result, SiTech and ASC gel have a somewhat lower average network chain molecular weight between crosslinks, a lower swell ratio, and a lower amount of extractables. (It should be noted that long-term biological testing of the Dow Corning gel is therefore a worst case situation

²⁹ G. M. Allen, Report Number CP 273 I, *Crosslink Density, Sol Fraction and Equilibrium Swell Ratio of Gel-Filled Mammary Prosthesis Gel*, January 21, 2003.

³⁰ C. S. Puckett, Report Number CP 361, *Sol Fraction, Equilibrium Swell Ratio, and Crosslink Density of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, February 6, 2003.

compared to testing SiTech gel because Dow Corning gel has fewer crosslinks and more extractables.)

TABLE 5-27. Comparisons of Dow Corning, SiTech, and ASC Gel Crosslinking, Swell Ratios and Percent Extractables (from Siltex Low-Bleed Devices, M:V ~ 1:100)

Gel (Report #)	M_c (g/mol)	ρ_c (mol/cm ³)	$\rho_c N_{AV}$ (chain/cm ³)	Swell Ratio	Extractables %
Dow Corning Gel (CP 273I)	18.3E+05 (4.1E+05)*	0.60E-06 (0.14E-06)	3.61E+17 (0.86E+17)	60.6 (7.8)	82.1 (1.9)
SiTech Gel (CP 361)	6.89E+05 (1.38E+05)	1.46E-06 (0.30E-06)	8.81E+17 (1.83E+17)	36.9 (4.0)	73.8 (3.5)
ASC Gel (CP 273I)	6.92E+05 (1.58E+05)	1.60E-06 (0.41E-06)	9.61E+17 (2.49E+17)	35.5 (4.5)	75.0 (3.1)

M_c = Network Chain Molecular Weight

ρ_c = Molar Crosslink Density

$\rho_c N_{AV}$ = Crosslink Chain Density

* - mean (standard deviation)

5.10.5.2 Extent of Crosslinking Comparison of PTC and SiTech Shells

The objective of this section is to describe and compare the extent of crosslinking measured on shells from PTC raw materials with the corresponding values for shells from SiTech raw materials.³¹ Results are shown in Table 5-28.

³¹ G. M. Allen, Report Number CP 273 II, *Crosslink Density, Sol Fraction and Equilibrium Swell Ratio of Gel-Filled Mammary Prosthesis Shell*, January 21, 2003.

Table 5-28. Comparisons of PTC Shell/NuSil Texture, SiTech Shell/NuSil Texture, and SiTech Shell/SiTech Texture Crosslinking, Swell Ratio and Percent Extractables (Shells from Finished Devices)

Shell/Texture (Report #)	M_c (g/mol)	ρ_c (mol/cm ³)	$\rho_c N_{AV}$ (chain/cm ³)	Swell Ratio	Extractables %
PTC/NuSil (CP 273II)	6303 (406)*	1.66E-04 (0.10E-04)	9.98E+19 (0.62E+19)	3.7 (0.02)	11.7 (0.5)
SiTech/NuSil (CP 273II)	6032 (176)	1.73E-04 (0.05E-04)	10.4E+19 (0.31E+19)	3.3 (0.03)	10.6 (0.4)
SiTech/SiTech (CP 361)	8400 (336)	1.31E-04 (0.05E-04)	7.90E+19 (0.32E+19)	3.7 (0.1)	8.3 (0.2)

M_c = Network Chain Molecular Weight

ρ_c = Molar Crosslink Density

$\rho_c N_{AV}$ = Crosslink Chain Density

* - mean (standard deviation)

The data indicate that the crosslinking, swell ratio, and extractable % results for textured PTC shells and textured SiTech shells are not substantially different.

5.10.6 Heavy Metals

5.10.6.1 Heavy Metals Content of Dow Corning, SiTech and ASC Gel

The objective of this section is to compare the heavy metals content of Dow Corning, SiTech, and ASC gels. The analysis was performed as described in Section 5.4 of this module. Report CP 279³² contains data on Dow Corning and ASC gel and report CP 360³³ contains current device SiTech gel data. The results for the gels are presented in Table 5-29.

³² Boggess, K. Report CP 279, *Heavy Metals Analysis of Gel Mammary Implants*, December 2, 1999.

³³ Julian, N. Report CP 360, *Extractable Metals Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, February 17, 2003.

Table 5-29. Heavy Metal Analysis of Dow Corning, SiTech, and ASC Gels

	Aqueous Extract, µg/g			Organic Extract, µg/g		
	Dow Corning	SiTech	ASC	Dow Corning	SiTech	ASC
Mg	ND	0.37	0.019	ND	ND	0.0074
Co	0.0016	0.06	0.0029	0.0014	ND	0.0013
Ni	0.12	0.048	0.048	0.015	0.0049	0.0061
Cu	0.043	0.0067	0.040	ND	0.018	0.0041
Zn	0.12	ND	0.094	ND	ND	ND
Mo	ND	ND	ND	ND	ND	ND
Ag	ND	ND	0.0035	ND	ND	ND
Cd	0.0019	0.0019	ND	ND	ND	ND
Sn	0.018	ND	0.015	0.084	ND	ND
Sb	0.0015	0.0025	0.0012	0.00095	0.010	0.0015
Ba	0.014	ND	0.015	0.0024	ND	ND
Pt	ND	0.018	ND	0.082	0.31	0.061
Pb	0.033	0.0085	0.040	ND	0.0019	ND
Be	ND	ND	ND	ND	ND	ND
Ti	ND	ND	0.0036	0.011	0.029	0.017
V	ND	ND	ND	ND	ND	ND
Cr	ND	ND	ND	ND	ND	ND
As	ND	ND	ND	ND	ND	ND
Be	ND	ND	ND	ND	ND	ND
Hg	ND	ND	ND	ND	ND	ND

With the exceptions of Co, Mg, Sn, Ti and Zn, the levels of the elements detected in most cases were similar in magnitude to those of the extraction fluids (solvent controls). From each type of gel, Dow Corning, SiTech, and ASC, the total metals from aqueous extracts (0.36 µg/g, 0.52 µg/g, and 0.28 µg/g respectively) and organic extracts (0.20 µg/g, 0.37 µg/g, and 0.10 µg/g respectively) were about equal.

Comparing the results, the Dow Corning gel, SiTech gel, and ASC gel are not substantially different in heavy metals content.

5.10.6.2 Heavy Metals Content of PTC Shells and SiTech Shells

The objective of this section is to compare the heavy metals content of shells from PTC raw materials with those of shells made from SiTech raw materials (see Table 5-30). Data on textured PTC material shells came from CP 279 while the textured SiTech material

shell data came from testing of the current PMA device (see Section 5.4 in this module).

TABLE 5-30. Heavy Metals Analysis of SiTech and PTC Shells (µg/g)

Element*	SiTech Shell		PTC Shell	
	Aqueous	Organic	Aqueous	Organic
Be	ND	ND	0.0041	ND
Mg	0.454	0.016	0.16	ND
Ti	ND	0.004	0.0028	0.012
V	ND	ND	ND	ND
Cr	ND	ND	ND	ND
Co	ND	ND	0.038	ND
Ni	0.017	0.010	ND	ND
Cu	0.024	ND	0.075	ND
Zn	0.126	0.011	0.13	ND
As	ND	ND	ND	ND
Se	ND	ND	ND	ND
Mo	ND	ND	ND	ND
Ag	ND	ND	0.047	ND
Cd	0.0024	0.0010	0.0032	ND
Sn	ND	ND	0.0041	ND
Sb	0.020	0.0016	0.0017	0.0037
Ba	0.0020	ND	0.0012	0.00089
Pt	0.055	0.078	0.0080	0.029
Hg	0.003	ND	ND	ND
Pb	0.015	0.0031	0.011	ND

With the exceptions of Co, Mg, Zn, Ti and, Sn the levels of the elements detected were similar in magnitude to those of the extraction fluids (solvent blanks). As will be discussed in detail in the toxicity risk analysis section of this module (Section 6.1), for those heavy metals which did not closely match levels in SiTech and PTC shells (e.g., Co, Mg, Zn, etc.), there are no toxicity issues associated with the observed values.

Based upon the heavy metals data and the toxicity risk analysis information, the PTC and SiTech shells are not substantially different in their heavy metals content.

5.10.7 Infrared Spectral Analysis

5.10.7.1 IR of Dow Corning, SiTech, and ASC Gels

The objective of this section is to compare the IR spectra of gel samples from finished sterile devices made by Dow Corning, SiTech, and ASC.^{34,35} The infrared spectra were obtained using a Fourier transformed infrared spectrophotometer (FT-IR) with an attenuated total reflectance accessory (ATR).

The spectra of the samples show identical absorbance maxima of gel samples from finished devices made with raw materials from the two sources. This technique is qualitative, and shows absorbance bands that are representative of the composition of silicone materials used in the finished devices. Specifically, the spectra are typical of polydimethylsiloxane, which is the prevalent moiety. There was no evidence of ----- character, which would show in the range of 3020 to 3080 cm^{-1} if present in sufficient amount to be detected. That would typically require the presence of a few percent of the ----- moiety in the composition.

The spectra demonstrate that the gel samples from finished devices made with Dow Corning, SiTech, and ASC raw materials are substantially equivalent.

³⁴ Grace Chiang, Report CP 280, *Surface Chemical Composition of Dow, ASC, and SiTech Gel-Filled Mammary Prostheses*, November 21, 1999, Appendix D, IR Spectra of Samples.

³⁵ Wenkai Ma, Report 362, *Infrared Spectral Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, February 10, 2003, Appendix C, IR Spectra of Samples.

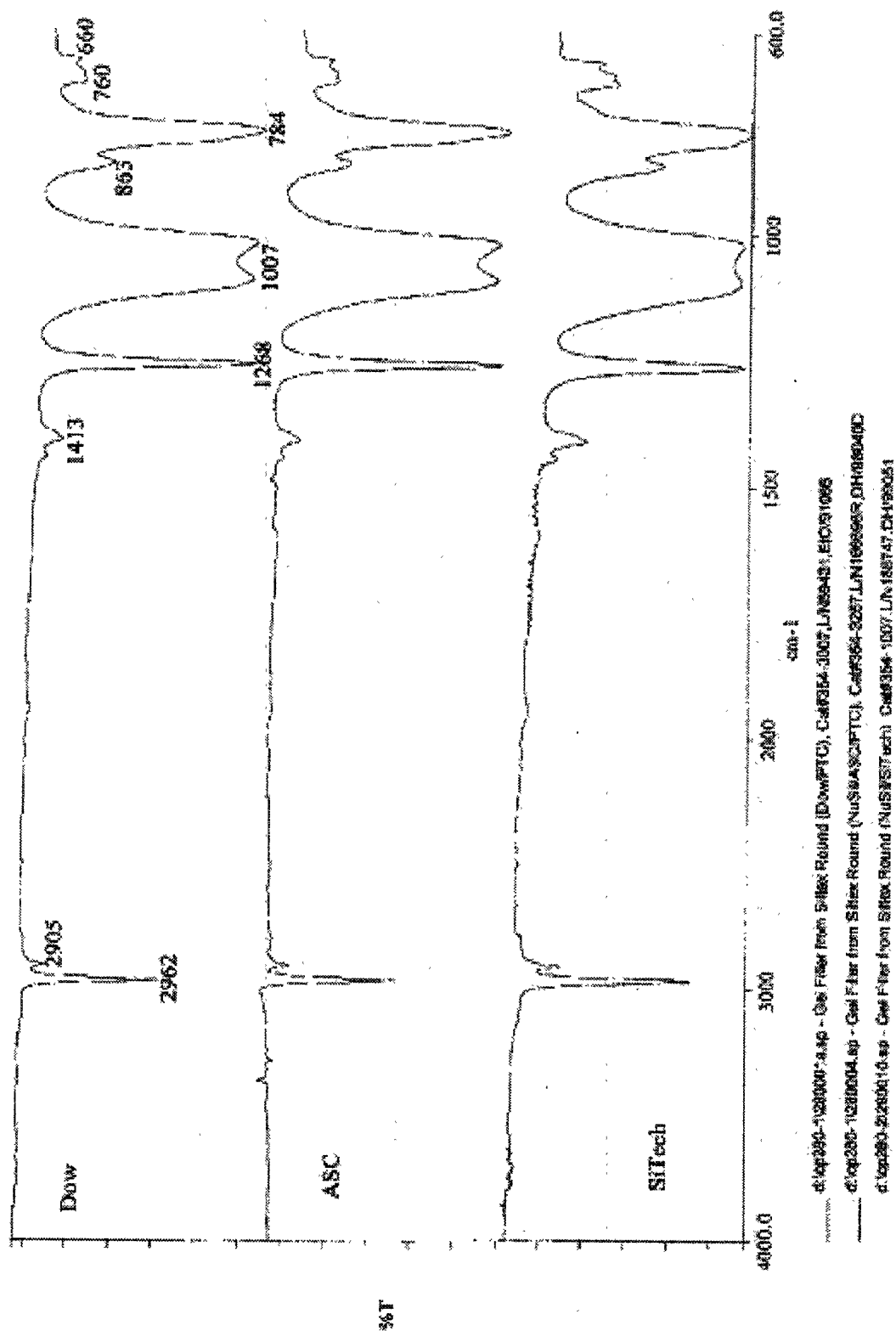


Figure 5-10 IR Spectral Comparison of Gel Fillers from Siltex Round Low-Bleed Devices (Dow, ASC and SiTech)

5.10.7.2 Infrared Spectral Analysis of PTC and SiTech Shells with NuSil and SiTech Texture Layers and Shell Patches

The objective of this section is to compare infrared spectra of shell samples from PTC and SiTech materials.^{36,37} The infrared spectra were obtained using a Fourier transformed infrared spectrophotometer (FT-IR) with an attenuated total reflectance accessory (ATR).

The spectra show identical absorbance maxima of shell samples from finished devices made with raw materials from the two vendors. This technique is qualitative, and shows absorbance bands that are representative of the composition of silicone materials used in the finished devices. Specifically, the spectra are typical of polydimethylsiloxane, which is the prevalent moiety in the composition of each material. There was no evidence of -----1 character, which would show in the range of 3020 to 3080 cm^{-1} if present in sufficient amount to be detected. That would typically require the presence of a few percent of the -----1 moiety at the surface of the material being analyzed. In shells the only -----1 containing component is an interior layer, from ----- silicone elastomer dispersion. It is surrounded by layers of dimethylsiloxane from dimethyl silicone elastomer dispersion used in the shell dipping process; therefore, the absence of ----- character by FT-IR ATR surface analysis is expected. No ----- character was observed in the other materials of the patch or texture layer, also as expected.

The results demonstrate that the elastomer samples from finished devices made with PTC and with SiTech shell dispersion materials are substantially equivalent when analyzed by FT-IR spectroscopy using ATR surface analysis.

³⁶ Grace Chiang, Report CP 280, *Surface Chemical Composition of Dow, ASC, and SiTech Gel-Filled Mammary Prostheses*, November 21, 1999, Appendix D, IR Spectra of Samples.

³⁷ Wenkai Ma, Report 362, *Infrared Spectral Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications*, February 10, 2003, Appendix C, IR Spectra of Samples.

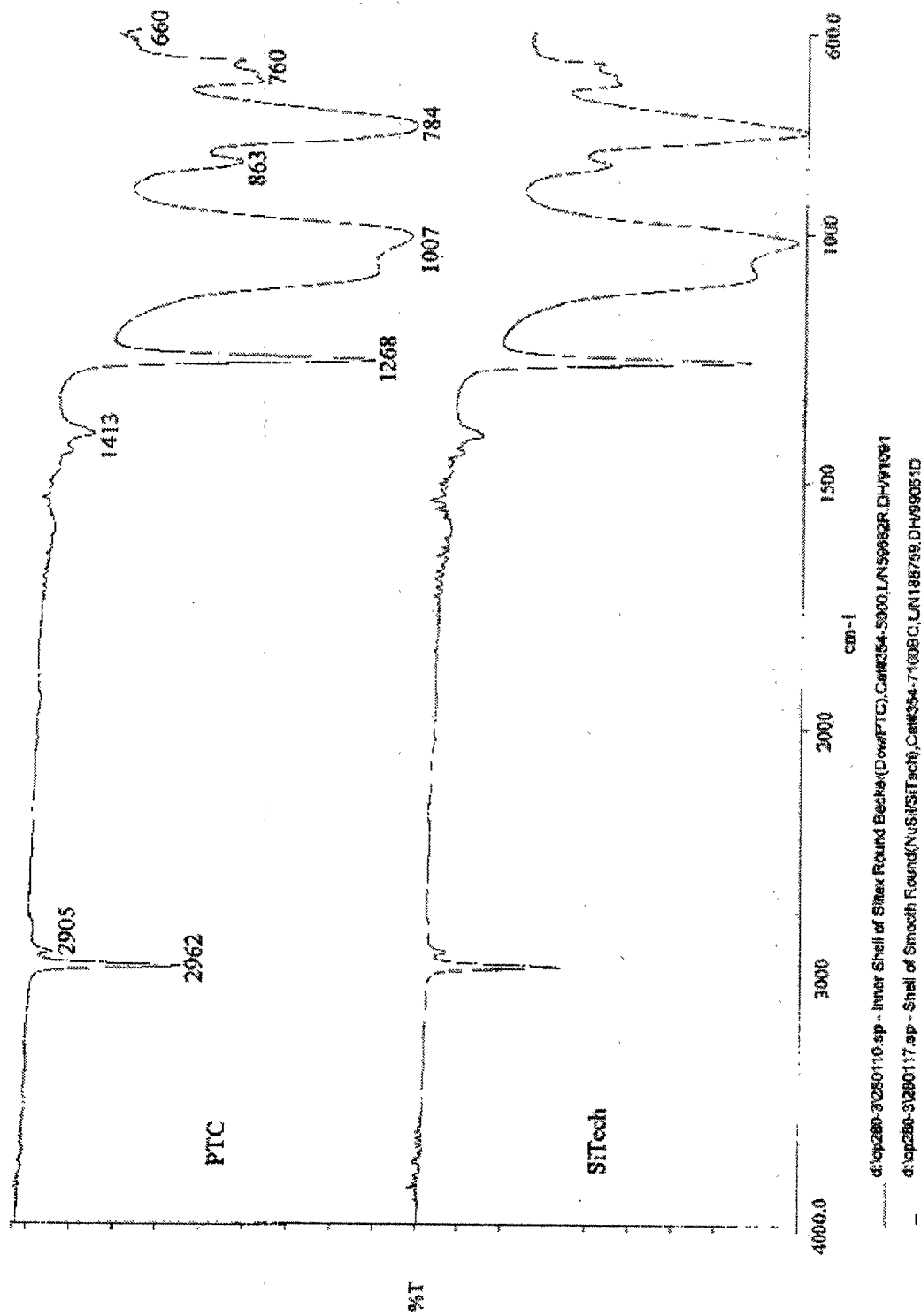


Figure 5-11 IR Spectra Comparison of HTC Smooth Shell (PTC vs SiTech)

5.11 Solvent Selection for Extractions on Samples from Finished Device

The extraction procedure was developed using ethanol for the polar solvent, and using methylene chloride and hexane for the non-polar solvents.^{38,39} Extraction samples were produced by static immersion of testing samples in the various solvents under controlled conditions. Calculations based upon gravimetric data yielded total extractables, percent recovery, etc. Siltex™ Round gel-filled devices (200 cc) were selected for testing as being representative of the gel-filled devices in this submission. The devices for this solvent selection testing were fabricated with NuSil Technology (for texturing, patch and patch components), Applied Silicone Corporation (for gel) and Polymer Technology Company (for shell) raw materials. The devices were selected from one device manufacturing lot. Static immersion extractions were performed on samples prepared from these devices with ethanol, methylene chloride and hexane as the test solvents. Each extraction was performed with three (3) samples and a method blank. Test devices were sterile, finished product.

Gel from ASC raw material yielded ~7%, ~78% and ~76% extractables with ethyl alcohol, hexane and methylene chloride solvents, respectively (see Table 5-31).

Serial extraction of gel samples with methylene chloride yielded an additional weight loss of ~9%, representing a cumulative quantity of extractables of ~85%. Typical recoveries were >95%. Typical relative standard deviations for extractable replicate measurements (n=3) were <5%.

Shell samples from NuSil/Polymer Technology Corporation raw materials (see Table 5-32) yielded ~5%, ~15% and ~15% extractables with ethyl alcohol, hexane and methylene chloride solvents, respectively. Typical recoveries were >95%. Typical relative standard deviations for extractable replicate measurements (n=3) were <5%.

Serial extraction of shell samples from finished devices with methylene chloride yielded an additional weight loss of ~0.2%, representing a cumulative quantity of extractables of ~15%. Typical recoveries were >95%. Typical relative standard deviations for extractable replicate measurements (n=3) were <5%.

The difference between the results of the two non-polar solvents was not statistically significant. Methylene chloride was chosen as the solvent of choice because it is amphiphilic (extracts polar and non-polar compounds) and is more suitable for chromatography. Methylene chloride was used in all testing except crosslink density testing, for which toluene was used.

³⁸ Allen, G. M. Report CP 274, Part I, *Extraction Solvent Comparison of Gel-Filled Mammary Prosthesis Gel*, May 27, 1999. Table II, Extraction Solvent Comparison of Siltex Round Low Bleed Gel-Filled Mammary Prosthesis Gel (Calculated Polymer Factor and Corrected Measurement Results).

³⁹ Allen, G. M. Report CP 274, Part II, *Extraction Solvent Comparison of Gel-Filled Mammary Prosthesis Shell*, May 27, 1999. Table II, Extraction Solvent Comparison of Siltex Round Low Bleed Gel-Filled Mammary Prosthesis Shell (Calculated Polymer Factor and Corrected Measurement Results).

Table 5-31. Extraction Solvent Comparison of ASC Gel from Siltex Round Low-Bleed Devices: Direct Gravimetric Weight Measurement Results

	Hexane	Methylene Chloride	Ethanol
Mean Average Extractables (%)	77.9	76.1	7.46
S	1.17	2.16	0.33
CV	0.02	0.03	0.04

s = Standard Deviation

CV = Coefficient of Variation

Table 5-32. Extraction Solvent Comparison of PTC Shells from Siltex Round Low-Bleed Devices: Direct Gravimetric Weight Measurement Results

	Hexane	Methylene Chloride	Ethanol
Mean Average Extractables (%)	15.0	14.91	4.92
S	0.18	0.96	0.13
CV	0.01	0.03	0.03

s = Standard Deviation

CV = Coefficient of Variation

6.0 TOXICITY RISK ANALYSIS

A toxicity risk analysis was conducted to assess the potential health risk posed by the extractables identified during testing of Mentor's Gel-filled Mammary Prostheses (see Section 5.1 Volatile Components through Section 5.4 Heavy Metals of this submission) if these compounds were to leach from the devices once implanted. The levels of metals,⁴⁰ siloxanes, and aromatic extractables identified during testing were compared, when possible, to established health risk-based standards, toxicity threshold levels identified in the published literature, and/or levels known to normally be present in the body. The following reasonable worst-case assumptions were used to arrive at exposure levels that could result if the compounds were released from the implant:

- All of the extractables from two maximum-size 800 cc silicone gel-filled implants (weighing 835 gm each) were released over a 30-day period.
- Extractables that were not detected were assumed to be present at the detection limit for that compound.

⁴⁰ Mentor's silicone gel-filled breast implants (both silicone elastomer shell and silicone gel filler) were analyzed for the presence of a wide range of potential metal residues (Be, Mg, Ti, V, Cr, Co, Ni, Cu, Zn, As, Se, Mo, Ag, Cd, Sn, Sb, Ba, Pt, Hg and Pb). Very sensitive analytical methods, employing both aqueous and organic extractions, yielded detection limits that ranged as low as 0.1 ppb for barium.

- The potential amount for metals present included the sum of aqueous and organic extractable metal in the whole device, if detected. In those cases where the value from the aqueous extraction was above the detection limit and nothing was detected in the organic extraction (or vice versa), the detection limit was used as the potential level for the non-detect measurement in calculating the sum of aqueous and organic extractable metal. Thus, the actual levels present in the whole device are most likely somewhat below the levels cited.
- A 60 kg woman has a total blood volume of 3.0 – 4.5 L (Burtis and Ashwood 1999).
- The following health-based standards and other criteria, where available, were used for comparison to levels of extractables found in Mentor's Gel-filled Mammary Prostheses:
- RfD = U.S. Environmental Protection Agency ("EPA") Reference Dose: "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (IRIS 2003).
- UL – Institute of Medicine Tolerable Upper Intake Level: "the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects to members of the healthy general population" (IOM 1997)
- MRL = Agency for Toxic Substances and Disease Registry ("ATSDR") Minimal Risk Level: "an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure" (ATSDR 2003).
- TLV-TWA = American Conference of Governmental Industrial Hygienists ("ACGIH") Threshold Limit Values – Time Weighted Average: "The time-weighted average concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed day after day, without adverse effect" (ACGIH 2001)
- NOAEL = No-observable-adverse-effect level.
- Published normal blood/serum levels.

The results of the toxicity risk analysis are provided below. These results demonstrate that, under conservative worst-case conditions, none of the levels of extractables identified during Mentor's testing exceed any recognized toxicity standard and/or level normally known to be present in the body. The Sponsor therefore concludes that the extractables identified in the Mentor Gel-filled Mammary Prostheses should not present a health risk if they were to leach from the implanted devices.

6.1 Metals (see Table 5-11 for the analytical data)

6.1.1 Beryllium (Be) was not detected (detection limit = 0.003 ppm) in either silicone elastomer shell or silicone gel. Using the assumptions listed above, the estimated reasonable worst-case daily exposure from two devices would be 0.36 µg beryllium. The oral RfD for beryllium is 0.002 mg/kg/day, equivalent to 120 µg/day for a 60 kg adult. Adjusting for absorption (3.7 percent in monkeys; ATSDR 2002), this RfD value is 12-fold higher than the estimated conservative worst-case exposure from Mentor silicone gel-filled implants.

6.1.2 Magnesium (Mg). The potential amount of magnesium present in a whole device was 0.391 µg/g, or 652 µg of magnesium per two devices, for an estimated reasonable worst-case daily exposure of 22 µg. For comparison, the normal serum of a 60 kg woman contains 54,000 µg of magnesium,⁴¹ an amount 80-fold higher than the total amount present in two maximum-size implants. Furthermore, the UL for magnesium is 350 mg/day (350,000 µg/day) for adults. Absorption of ingested magnesium is inversely proportional to the ingested amount; 40-60 percent of a 380 mg dose is absorbed (IOM 1997). Assuming 50 percent absorption, the daily absorbed amount of magnesium corresponding to the UL is 290-fold higher than the total amount present in two maximum-size implants.

6.1.3 Titanium (Ti). The potential amount of titanium present in a whole device was 0.0326 µg/g, or 54 µg of titanium per two devices, for an estimated reasonable worst-case daily exposure 1.8 µg titanium. For comparison, the human body contains approximately 15,000 µg of titanium, primarily localized in the lungs (HSDB 2003). With respect to potential toxicity of titanium, peer-reviewed information from the Hazardous Substances Data Bank (HSDB 2003) notes that:

"The extremely low toxicity of titanium and several of its compounds (titanium salicylate, oxides, peroxide, and tannate) when in contact with skin and tissues has been demonstrated by its use in the therapy of skin disorders. The biocompatibility of titanium is high as shown by its vast use as an implant material in orthopedics, oral surgery, and neurosurgery. The small amounts of titanium occasionally released from implants into adjacent tissues have not caused any adverse effects."⁴²

⁴¹ The normal serum magnesium concentration is 1.8 to 2.3 mg/dL (IOM 1997).

⁴² Friberg, L., Nordberg, G.F., Kessler, E. and Vouk, V.B. (eds). Handbook of the Toxicology of Metals. 2nd ed. Vols I, II.: Amsterdam: Elsevier Science Publishers B.V., 1986.,p. V2 602

6.1.4 Vanadium (V) was not detected (detection limit = 0.14 – 0.16 ppm) in either silicone elastomer shell or silicone gel. Using the assumptions listed above, the estimated reasonable worst-case daily exposure would be 16.8 µg vanadium. The oral RfD for vanadium is 0.009 mg/kg/day, equivalent to 540 µg/day for a 60 kg adult. Adjusting for absorption (16 percent; Azay et al. 2001), this RfD value is 5-fold higher than the estimated conservative worst-case exposure from Mentor silicone gel-filled implants.

6.1.5 Chromium (Cr). The potential amount of chromium present in a whole device was 0.0288 µg/g, or 48 µg of chromium per two devices, for an estimated reasonable worst-case daily exposure of 1.6 µg chromium. For comparison, the whole blood of a 60 kg woman contains 60 to 135 µg of chromium.⁴³ Chromium exists primarily in one of three oxidation states: the zero, trivalent and hexavalent states. Trivalent chromium oxide is the dominant naturally occurring form of chromium (Barnhart 1997). The oxide that forms on the surface of stainless steel, trivalent chromium oxide, is in fact largely responsible for its inert nature (Barnhart 1997). It should be noted that no hexavalent chromium compounds are used in the manufacture of silicone breast implants. Therefore, the relevant toxicity standard to apply is the RfD for trivalent chromium (1.5 mg/kg/d – oral administration), equivalent to 90,000 µg/day for a 60 kg adult. Adjusting for absorption (0.5 percent in monkeys; U.S. EPA 1998), this RfD value is 280-fold higher than the estimated conservative worst-case exposure from Mentor silicone gel-filled implants.

6.1.6 Cobalt (Co). The potential amount of cobalt present in a whole device was 0.052 µg/g, or 87 µg of cobalt per two devices, for an estimated reasonable worst-case daily exposure of 2.9 µg cobalt. Cobalt is frequently used as a component of alloys used for medical implants. Cobalt is also an essential cofactor in vitamin B₁₂, and is therefore an essential micronutrient (Burtis and Ashwood 1999). The normal serum of a 60 kg woman contains 0.3-2.0 µg of cobalt.⁴⁴ The MRL for intermediate exposure to cobalt corresponds to an exposure level of 600 µg/day in a 60 kg adult woman. Adjusting for absorption (18-97 percent of orally administered dose; ATSDR 2003), the MRL is 37- to 200-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

⁴³ In persons "without excess exposure," the normal chromium concentration in whole blood is 20 to 30 µg/L (Klassen 2001).

⁴⁴ The normal serum cobalt concentration is 0.11 to 0.45 µg/L (Burtis and Ashwood 1999).

6.1.7 Nickel (Ni). The potential amount of nickel present in a whole device was 0.0496 µg/g, or 83 µg of nickel per two devices, for an estimated reasonable worst-case daily exposure of 2.8 µg nickel. For comparison, whole blood of a 60 kg woman contains 3.0 to 126 µg of nickel.⁴⁵ The UL for nickel is 1.0 mg/day (1,000 µg/day) for adults. Absorption of ingested nickel is quite low, with several estimates of 1 to 10 percent (HSDB 2003, IOM 2002), thus the absorbed amount of nickel corresponding to the UL would be 10 to 100 µg/day, or 3.6- to 36-fold higher than the 2.8 µg potential reasonable worst-case daily exposure from two maximum-size implants. The RfD for nickel is 0.02 mg/kg/day, equivalent to 1200 µg/day for a 60 kg adult. Adjusting for absorption, this RfD value is 4.3- to 43-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

6.1.8 Copper (Cu). The potential amount of copper present in a whole device was 0.0247 µg/g, or 41 µg of copper per two devices, for an estimated reasonable worst-case daily exposure of 1.4 µg copper. For comparison, the normal serum of a 60 kg woman contains 2400 to 7000 µg of copper.⁴⁶

6.1.9 Zinc (Zn). The potential amount of zinc present in a whole device was 0.0344 µg/g, or 57 µg of zinc per two devices, for an estimated reasonable worst-case daily exposure of 1.9 µg zinc. For comparison, the normal serum of a 60 kg woman contains 2100 to 5400 µg of zinc.⁴⁷ The RfD for zinc is 0.3 mg/kg/day, equivalent to 18,000 µg/day for a 60 kg adult. Adjusting for absorption (25-90 percent, HSDB 2003), this RfD value is 2300- to 8500-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

6.1.10 Arsenic (As) was not detected (detection limit = 0.05 - 0.07 ppm) in either silicone elastomer shell or silicone gel. Using the assumptions listed above, the estimated reasonable worst-case daily exposure would be 6.8 µg arsenic. For comparison, whole blood of a 60 kg woman normally contains 6 to 104 µg of arsenic, and a level of 1800 to 41,800 µg is associated with acute poisoning.⁴⁸

6.1.11 Selenium (Se) was not detected (detection limit = 0.02 – 0.05 ppm) in either silicone elastomer shell or silicone gel. Using the assumptions listed above, the estimated reasonable worst-case daily exposure would be 3.8 µg

⁴⁵ The normal nickel concentration in whole blood is 1.0 to 28.0 µg/L (Burtis and Ashwood 1999).

⁴⁶ The normal serum copper concentration for adult women is 80-155 µg/dL (Burtis and Ashwood 1999).

⁴⁷ The normal serum zinc concentration is 70-120 µg/dL (Burtis and Ashwood 1999).

⁴⁸ The normal serum concentration of arsenic in whole blood is 2-23 µg/L, while the concentration associated with acute poisoning is 600-9300 µg/L (Burtis and Ashwood 1999).

selenium. For comparison, whole blood of a 60 kg woman normally contains 1740 to 10,530 µg of selenium.⁴⁹

6.1.12 Molybdenum (Mo) was not detected (detection limit = 0.0003 - 0.0006 ppm) in either silicone elastomer shell or silicone gel. Using the assumptions listed above, the estimated reasonable worst-case daily exposure would be 0.052 µg molybdenum. For comparison, the serum of a 60 kg woman normally contains 0.3 to 13.5 µg of molybdenum.⁵⁰

6.1.13 Silver (Ag) was not detected (detection limit = 0.0003 - 0.0007 ppm) in either silicone elastomer shell or silicone gel. Using the assumptions listed above, the estimated reasonable worst-case daily exposure would be 0.056 µg silver. The RfD for silver is 0.005 mg/kg/day, equivalent to 300 µg/day for a 60 kg adult. Adjusting for absorption (4 percent, IRIS 2003), this RfD value is 200-fold higher than the estimated conservative worst-case exposure from Mentor silicone gel-filled implants.

6.1.14 Cadmium (Cd). The potential amount of cadmium present in a whole device was 0.0025 µg/g, or 4.2 µg of cadmium per two devices, for an estimated reasonable worst-case daily exposure of 0.14 µg cadmium. For comparison, the normal serum of a 60 kg woman contains 0.9 to 5.4 µg of cadmium.⁵¹ The RfD for cadmium is 0.0005 mg/kg/day, equivalent to 30 µg/day for a 60 kg adult. Adjusting for absorption (5 percent, HSDB 2003), this RfD value is 10-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

6.1.15 Tin (Sn) was not detected (detection limit = 0.001 - 0.003 ppm) in either silicone elastomer shell or silicone gel. Using the assumptions listed above, the estimated reasonable worst-case daily exposure would be 0.24 µg tin. For comparison, the blood of a 60 kg woman normally contains 1.2 to 2.9 µg of tin.⁵²

6.1.16 Antimony (Sb). The potential amount of antimony present in a whole device was 0.0137 µg/g, or 23 µg of antimony per two devices, for an estimated reasonable worst-case daily exposure of 0.76 µg antimony. The RfD for antimony is 0.0004 mg/kg/day, equivalent to 24 µg/day for a 60 kg adult. This RfD value is 30-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

6.1.17 Barium (Ba). The potential amount of barium present in a whole device was 0.00058 µg/g, or 0.97 µg of barium per two devices, for an

⁴⁹ The concentration of selenium in whole blood is 58-234 µg/dL (Burtis and Ashwood 1999).

⁵⁰ The normal serum concentration of molybdenum is 0.1-3.0 µg/L (Burtis and Ashwood 1999).

⁵¹ The normal serum cadmium concentration is 0.3-1.2 µg/L (Burtis and Ashwood 1999).

⁵² The normal serum concentration of tin is 0.4-0.64 µg/L (Tietz 1995).

estimated reasonable worst-case daily exposure of 0.032 μg barium. The RfD for barium and its compounds is 0.07 mg/kg/day, equivalent to 4200 μg /day for a 60 kg adult. Soluble barium salts (all of the barium detected in the silicone elastomer shell was aqueous extractable) are rapidly and well absorbed (HSDB 2003). This RfD value is 130,000-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

6.1.18 Platinum (Pt). The potential amount of platinum present in a whole device was 0.299 $\mu\text{g/g}$, or 499 μg of platinum per two devices, for an estimated reasonable worst-case daily exposure of 17 μg platinum. As discussed previously in the Biological Module of this PMA submission, the Institute of Medicine (Bondurant et al. 1999) noted that Stein et al. (1999) reported that "the platinum in breast implants is in zero valence form in the final cured state in excess vinyl." Platinum in the zero valence state exhibits relatively low toxicity and is recognized to be several orders of magnitude less toxic than soluble platinum salts (e.g., ACGIH 2001). IOM (1999) also pointed out that "many silicone-containing implants other than breast implants (listed in Chapter 2) are found at high frequency in the general population and presumably contain platinum also; the committee is not aware of any evidence that platinum toxicity is present in these persons." The IOM report went on to conclude that "[s]ome have speculated that platinum found in silicone gel and elastomer may be responsible for allergic disease in women with silicone breast implants. Very little platinum, microgram quantities, is present in implants, most investigators believe it to be in the zero valence state (see Section VI of this submission), and it likely diffuses through the shell at least over a considerable period of time. Evidence for resulting systemic disease at such exposures is lacking." The TLV-TWA for platinum metal (zero valence state) is 1 mg/m³, which translates to a daily exposure of 10,000 μg , as compared with the estimated reasonable worst-case daily exposure from silicone gel-filled implants of 17 μg total platinum. Approximately 92 percent of the total platinum detected in the silicone gel-filled implants was organosoluble, consistent with the presence of a zero valence state platinum catalyst. The balance of the platinum detected, 7.6 percent, was aqueous-soluble, equivalent to a reasonable worst-case daily exposure from silicone gel-filled breast implants of 1.3 μg . This aqueous-soluble platinum, measured at 23 ppb, might represent very minute solubility of the zero valence platinum catalyst, or as a worst case, soluble platinum salt(s). The TLV-TWA for platinum soluble salts is 0.002 mg/m³, which translates to a daily exposure of 20 μg , as compared with an estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants of 1.3 μg aqueous-soluble platinum.

6.1.19 Mercury (Hg). The potential amount of mercury present in a whole device was 0.0039 $\mu\text{g/g}$, or 6.6 μg of mercury (non-organic) per two devices, for an estimated reasonable worst-case daily exposure of 0.22 μg mercury.

For comparison, the normal serum of a 60 kg woman contains 1.8 to 265 µg of mercury.⁵³ The MRL is 0.0003 mg/kg/day for chronic exposure to mercury (in its most toxic form, methylmercury). It should be emphasized that the form of mercury detected in silicone gel-filled implants was not organosoluble, and thus would be expected to be considerably less toxic than methylmercury. The MRL for chronic exposure to methylmercury corresponds to an exposure level of 18 µg/day in a 60 kg adult woman, a level that is more than 80-fold higher than the estimated reasonable worst-case aqueous-soluble mercury exposure from Mentor silicone gel-filled implants.

6.1.20 Lead (Pb). The potential amount of lead present in a whole device was 0.011 µg/g, or 19 µg of lead per two devices for an estimated reasonable worst-case daily exposure of 0.63 µg lead. The U.S. Department of Health and Human Services (DHHS) recommends "that blood lead levels be reduced to <25 µg/dL among all adults as a preventive health measure" (Roscoe et al. 2002). Women of child-bearing age are advised by ACGIH that blood lead levels >10 µg/dL may result in offspring exposure at CDC's pediatric concern level of >10 µg/dL (Roscoe et al. 2002). This CDC action level for lead in blood of 10 µg/dL corresponds to a total blood level of 300 to 450 µg in a 60 kg adult woman, which is 480- to 710-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

6.2 Siloxanes

6.2.1 D₄ (octamethylcyclotetrasiloxane).

The potential amount of D₄ present in a whole device was 0.47 µg/g, or 785 µg of D₄ per two devices, for an estimated reasonable worst-case daily exposure of 26 µg D₄. As discussed in the previously submitted Biological Module of this PMA, a no-observable-adverse-effect level (NOAEL) of 1.05 mg D₄/kg body weight/day was derived from Klykken et al. (1999) and Plotzke et al. (2000), equivalent to 63,000 µg/day for a 60 kg adult. This NOAEL is 2,400-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

As discussed in the previously submitted Biological Module of the PMA, a state-of-the-art pharmacokinetic study of ¹⁴C-octamethylcyclotetrasiloxane (D₄) in Fischer 344 rats after single and multiple exposures to 7, 70 or 700 ppm was recently published by Plotzke et al. (2000). Data from this study formed the basis for development of a physiologically-based pharmacokinetic (PBPK) model for D₄ by Anderson et al. (2001) which concluded that "high pulmonary and hepatic clearance, coupled with induction of metabolizing

⁵³ The normal concentration of platinum in whole blood of persons from the U.S. is 0.49-1.8 µg/L (HSDB 2003).

enzymes at high exposure concentrations, rapidly remove free D₄ from the body and ensure that there is no accumulation on multiple exposures." Luu and Hutter (2001) published a different PBPK model for D₄ that challenged the Anderson et al. (2001) findings and predicted accumulation following multiple exposures. Numerous apparent flaws in the methodology of Luu and Hutter, however, have been asserted by Meeks (2002) and Andersen et al. (2002). Meeks (2002), in his critique, reported actual measured concentrations of D₄ in blood and fat from rats exposed to 700 ppm D₄ by inhalation (6hr/day, 5 days/week) for 15 days and 6 months, which "confirm that D₄ does not accumulate in the body." In order to assess the validity of the competing claims, Mentor Corporation sought out an independent evaluation of the competing models by an internationally-recognized PBPK modeler. A brief review by Harvey Clewell is included in the Appendices to this module (as is his curriculum vitae). This critique identified serious deficiencies in the Luu and Hutter methodology that raise serious doubts about any of their conclusions. Clewell notes that:

"Even apart from the question of the validity of the model, there is reason to question the conclusions reached by Luu and Hutter on the basis of their evaluation of the experimental data and the predictions of the model. Unfortunately, they do not appear to be well grounded in pharmacokinetics. For example, they repeatedly refer to the pharmacokinetic behavior of D₄ as nonlinear. Not only is the data for D₄ clearly consistent with linear kinetics (see, for example, Figure 2 and Table 5 in Plotzke et al. 2000), but also the model that Luu and Hutter use to describe the data is a linear model. Contrary to their interpretations, there is simply no evidence for significant saturation of elimination. Moreover, what they refer to as accumulation in the fat for repeated dosing is simply a slow time constant for equilibration. They clearly do not understand that the determinant of long-term retention for chemicals such as D₄ is not the extent to which they partition into the fat but the rate of metabolic and exhalation clearance. The persistence of nonvolatile chemicals such as dioxin and PCBs is due to their low metabolic clearance and the absence of exhalation clearance. D₄, in contrast, is rapidly exhaled and well metabolized, so that, similar to such chemicals as styrene and perchloroethylene, its persistence is low."

"Given the limitations of the model and the inexpertise of the authors, there can be little confidence in any conclusions presented regarding the potential bioaccumulation of D₄ from breast implants."

Thus, the findings of Andersen et al. (2001) retain validity in demonstrating that "high pulmonary and hepatic clearance, coupled with induction of metabolizing enzymes at high exposure

concentrations, rapidly remove free D₄ from the body and ensure that there is no accumulation on multiple exposures."

6.2.2 D₅ (decamethylcyclopentasiloxane).

The potential amount of D₅ present in a whole device was 2.47 µg/g, or 4,125 µg of D₅ per two devices, for an estimated reasonable worst-case daily exposure of 138 µg D₅. As discussed in the previously submitted Biological Module of this PMA, a no-observable-adverse-effect level (NOAEL) of 14 mg D₅/kg body weight/day was derived from Burns-Naas et al. (1998) and Plotzke et al. (2000), equivalent to 840,000 g/day for a 60 kg adult. This NOAEL is 6,000-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

The available toxicological data on permethylated cyclic siloxanes (D₄ through D₂₁) focuses almost exclusively on D₄ and D₅, which are believed to exhibit the greatest toxicity and biological activity in the series. The aqueous solubility, toxicity and biological activity of permethylated cyclic siloxanes decreases with increasing size. A study by Varaprath et al. (1993) demonstrated that the aqueous solubility of D₅ is 4.2-fold lower than that of D₄, while the aqueous solubility of D₆ is 4.0-fold lower than that of D₅. The NOAEL for D₅ is 14-fold higher than that for D₄. In an adjuvancy study (Klykken 1999), the observed activity decreased significantly in the series D₄>D₅>D₆>D₇. D₅ was 3.0-fold less active than D₄; D₆ was 3.9-fold less active than D₅; and D₇ was 1.7-fold less active than D₆. Higher MW cyclics, which are also less mobile, thus represent a reduced toxicity potential as compared with the lower MW cyclics (e.g., D₄ and D₅). Based on the comparative information described above, similar exposure analyses of the series D₆-D₂₁ were performed, assuming a 1.4-fold reduction in potency with each increase in cyclic size (e.g., D₆ exhibiting 1.4-fold less potency than D₅). The 1.4-fold factor was conservatively selected as one-tenth the actual 14-fold reduction in potency observed between D₄ and D₅. The results for D₆-D₂₁ of such analyses revealed reasonable worst-case exposures from Mentor silicone gel-filled implants that ranged between 1500- to 7400-fold lower than estimated no-effect levels.

6.2.3 -----

----- is used in the manufacture of the -----copolymer elastomer employed in the low-bleed shells of Mentor silicone gel-filled mammary prostheses. The amount of ----- present in a whole device was 70 µg/g (70 ppm). As part of Mentor's overall safety testing program for this device, both short- and long-term preclinical testing of the -----copolymer elastomer has been performed. The results of this testing, which did not reveal any significant adverse effects, were included in the previously-

submitted Biological module of this PMA. - has itself been tested for genotoxic potential in Ames mutagenicity assays by both Dow Corning and Litton Bionetics and showed no evidence of mutagenicity (Toxline 2003). Furthermore, the concentration of - in the finished sterilized devices (70 ppm) is below the toxicity thresholds for both relatively non-toxic compounds (15,000 ppm) and relatively toxic compounds (100 ppm) set forth in the 1995 CDRH Draft Guidance for the Biological Evaluation of Materials. As the 1995 Guidance noted, "since the thresholds for identification and quantification are based on systemic toxicity concerns, any constituent present in the finished device or an extract of the finished device at levels less than the threshold will be considered to have met the systemic toxicity testing requirements."

6.3 *Aromatics*

6.3.1 **Xylene.**

The potential amount of xylene present in a whole device was 0.080 µg/g, or 134 µg of xylene per two devices, for an estimated reasonable worst-case daily exposure of 4.5 µg xylene. As discussed in the previously submitted Biological Module of this PMA, the RfD for xylene is 2 mg/kg/day, equivalent to 120,000 µg/day for a 60 kg adult. Adjusting for absorption (87-92 percent of orally administered dose; ATSDR 2003), this RfD value is 23,000- to 24,500-fold higher than the estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants.

7.0 SUMMARY AND CONCLUSION

This chemical testing PMA module has presented data to characterize Mentor's Gel-filled Mammary Prosthesis and its major components (shell and gel). Testing was performed in accordance with FDA's Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Guidance for Industry and FDA (February 11, 2003) whenever possible. The data were used for a toxicity risk analysis of the chemical compounds extracted from the device, verification that certain manufacturing changes did not cause significant changes in the chemical extractables profile of the device, and to support Mentor's conclusion that long term biological safety testing performed on gel-filled mammary devices and components made with prior vendor silicone materials is still directly applicable to the devices in this PMA submission.

The chemical testing consisted of a total extractables quantitation coupled with detailed qualitative and quantitative analyses of the volatile and semivolatile compounds, and a mostly qualitative nonvolatile extractables analysis. The analytical techniques utilized included gravimetry for overall extractables, dynamic headspace purge/trap with gas chromatography/mass spectroscopy (P/T-GC/MS) for volatiles, direct liquid injection gas chromatography/mass spectroscopy (GC/MS) for semivolatiles, and liquid injection gel permeation chromatography (GPC) for nonvolatiles. Compounds up to 1500 molecular weight were targeted for identification and quantitation.

In addition to the above extract testing, determination of extractable heavy metals, component crosslink densities, and surface composition analysis were conducted. Where necessary, a solvent extraction comparison and verification of exhaustive solvent extraction were performed. All sample preparation and analysis methods were validated by including spiked recovery of selected analytes and assessment of quantitation methods for linearity, precision, and detection limits. Reference libraries of standard compounds were developed from consideration of raw materials, additives, synthesis byproducts and manufacturing process aids and were used for positive identification of extractable compounds.

The data showed that the gel-filled mammary devices being submitted in this PMA are chemically not substantially different from earlier gel-filled mammary prostheses Mentor has manufactured and performed safety testing on in the past or for which testing has been published in the literature. In particular, Mentor's current gel (manufactured by SiTech, LLC) has been compared to the Dow Corning gel, on which most of the original safety testing was performed, in order to show that the existing biological safety testing is directly applicable to the SiTech gel. SiTech has provided a side-by side evaluation of the two gels in its Master Access File for their Gel-2167/Gel-2168 (MAF #1039) using the tests required by FDA's "Guidance for the Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials" (July 1993). These tests demonstrated that the SiTech gel is not substantially different from the Dow Corning Gel Q7-2167/Q7-2168. Additionally, the processes used to fabricate Mentor's gel-filled mammary devices did not need to be changed in order to convert from using the Dow Corning gel to the SiTech gel.

In addition to gel testing, Mentor has performed sterile finished product extractables testing on devices made with both SiTech and Dow Corning gels and has determined that the finished products are not substantially different. This means that the profile of the device extractables is similar for the two devices. The SiTech gel taken from a device has less overall extractables, less volatile compounds, slightly more cross-linked (based on gel volume), similar quantities of most semivolatile compounds, similar extractable nonvolatile materials based upon their molecular weights, no significant differences in their heavy metals content, and similar FTIR profiles when compared to the Dow Corning gel taken from devices. Because of these comparative results, Mentor believes that the safety testing data on Dow Corning's Q7-2167/Q7-2168 gel is directly applicable to SiTech, LLC's Gel-2167/Gel-1268 when used in Mentor's Gel-filled Mammary Prostheses. The gel materials are not substantially different by all criteria established in FDA's "Guidance for the Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials" (July 1993).

[Besides the above comparative testing, it needs to be noted that Mentor has provided similar comparative extractables data of SiTech gel to Applied Silicone Corporation (ASC) gel from sterile devices. Even though ASC gel has higher extractables, in the potentially more significant lower molecular weight range when compared to Dow Corning and SiTech gel, the ASC gel has been tested for long-term toxicity with no unaccounted for adverse effects (see Master Access File #645). This set of findings combined with the Dow Corning gel safety testing provides strong evidence of the lack of any potential long term adverse effects with the SiTech gel.]

The chemical data provided also demonstrates that gel-filled mammary shells made with SiTech dispersion materials are not substantially different from shells which were made from PTC dispersion materials and which were used in chronic toxicity/carcinogenicity, reproductive and teratology, immunotoxicity, and adjuvancy testing. The results show that for volatiles, total extractables, semivolatile extractables, nonvolatile extractables, crosslink density (including swell), heavy metals and IR spectra data, the SiTech shell is substantially equivalent to the PTC shell in type and quantity of extractables and chemical characteristics. This would be expected since SiTech's formulation for the methyl and ----- dispersions were based directly upon PTC's specific formulations.

In addition to the safety testing of the gels and shells, the toxicity risk analysis on the extractable compounds from Mentor devices made with SiTech gel, shell, and ----- elastomer has shown that there are no compounds extracted from a gel-filled mammary device in a quantity which might pose any toxicological concern when compared to the published toxicity information for those materials.

Information was provided on the issue of platinum extractables and the valence state of the platinum. Review of the published literature indicates that both theoretically and based upon available experimental data, the valence state of the platinum in platinum catalyzed silicone materials is zero, the least toxic of the different platinum valence states.

Data were provided showing that the change in dipping mandrel material from ----- to ----- and the use of laser marking on the device patch to provide identification information did not cause any appreciable changes in the device extractables profile.

The chemical testing data in this module of Mentor's Gel-filled Mammary Prosthesis PMA strongly support the safety of this device for its intended use and strongly support the relevance of all the biological testing data in this PMA to Mentor's current PMA devices.